Heparin-induced thrombocytopenia in cardiac surgery and critically ill patients

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Summary

Thrombocytopenia as well as anti-platelet factor 4/heparin (PF4/H) antibodies are common in cardiac surgery patients and those treated in the intensive care unit. In contrast, heparin-induced thrombocytopenia (HIT) is uncommon in these populations (~1 % and ~0.5 %, respectively). A stepwise approach where testing for anti-PF4/H antibodies is performed only in patients with typical clinical symptoms of HIT improves diagnostic specificity of the laboratory assays without losing sensitivity, thereby helping to avoid overdiagnosis and resulting HIT overtreatment. Short-term re-exposure to heparin, especially given intraoperatively for cardiovascular surgery, is a reasonable therapeutic option in patients with a history of HIT who subsequently test negative for HIT antibodies. Organ failure(s), enhanced bleeding risks, and other characteristics require special considerations regarding non-heparin anticoagulation: Argatroban is the alternative anticoagulant with pharmacokinetics independent of renal function, but it has a prolonged half-life in case of impaired liver function. For bivalirudin, protocols during cardiopulmonary bypass surgery are established, and it is suitable for patients with liver insufficiency. A major issue of direct thrombin inhibitors are false high activated partial thromboplastin time values in patients with comorbidities affecting prothrombin, which can result in systematic underdosing of the drugs. This is not the case for danaparoid and fondaparinux, which can be monitored by anti-factor Xa assays, but have long half-lives and no suitable antidote. This review includes also information on management of on- and off-pump cardiac surgery, ventricular assist devices, percutaneous interventions, continuous renal replacement therapy, and extracorporeal membrane oxygenation in patients with HIT.

Keywords

Heparin-induced thrombocytopenia, intensive care unit, cardiac surgery

Introduction

Patients who have undergone cardiac surgery (CS), as well as critically ill patients, have in common the observation that frequencies of forming anti-platelet factor 4/heparin (anti-PF4/H) antibodies are much higher than clinically-evident heparin-induced thrombocytopenia (HIT) (1, 2). Further, thrombocytopenia with platelet counts <100×10⁹/l develops in up to ≈40 % of these patients (3, 4). This results in a high likelihood for a coincidence of thrombocytopenia and anti-PF4/H antibodies, i.e. the antibodies are usually not the cause of the low platelet count. Therefore, the diagnosis of HIT in such patients is challenging. Moreover, as heparin represents the usual first-line anticoagulant for both patient populations, HIT is a relevant patient safety issue. This review aims to summarise special aspects of the diagnostic and therapeutic approaches of HIT in CS and intensive care unit (ICU) patients.

Cardiac surgery

Prevalence and clinical relevance of anti-PF4/heparin antibodies

When patients are screened systematically before CS, some studies find that up to approximately 20 % test positive for anti-PF4/H antibodies by enzyme-immunoassay (EIA) (5–7). By day 10 after surgery, the prevalence of these antibodies increases to 50–75 % (1, 4, 8, 9). The overall incidence of HIT in post-CS patients is, however, only ≈1 % (4, 9, 10). This raised two issues: first, what is the relevance of preexisting antibodies for the outcome in patients scheduled for CS with heparin exposure? and second what is the relevance of these antibodies developing after CS?

Impact of anti-PF4/heparin antibodies detected by screening before CS on patient outcome

The prevalence of anti-PF4/H antibodies detected by screening before CS was 5–22 % in several studies (11) (Table 1). Most of
these antibodies seem to be of the immunoglobulin (Ig) M class (5). These antibodies, however, cannot activate platelets via the platelet FcγRIIa (IgG) receptors when heparin is given during and after cardiopulmonary bypass (CPB) surgery (12, 13). Accordingly, none of the studies found an increased incidence of acute HIT in these patients, compared to patients testing negative for anti-PF4/H antibodies at preoperative baseline. However, anti-PF4/H antibodies of any Ig class were associated with worse outcomes in three studies (7, 14, 15), while others found no higher risk for thrombocytopenia or thrombotic events (1, 5, 6) (Table 1).

Based on these data, preoperative screening for anti-PF4/H antibodies of patients scheduled for CS is strongly discouraged, with two exceptions: i) patients who develop clinical features of HIT during pre-surgery heparin treatment (16), and ii) patients with a history of HIT, to decide whether heparin re-exposure is feasible (see below).

**Impact of anti-PF4/H antibodies detected by screening after CS on patient outcome**

In post-CPB patients without HIT, anti-PF4/H antibodies were associated with thromboembolic complications (15, 17, 18), infections, acute kidney failure, and higher mortality (18). However, other studies found no association between positive anti-PF4/H antibody status and any adverse outcome (1, 6, 19) (Table 2). The uncertain prognostic value of anti-PF4/H antibodies after CPB argues that testing for HIT antibodies should be restricted to patients who present with typical clinical symptoms of HIT, since these patients will require alternative anticoagulation if HIT antibodies are present (16).

**Diagnosis of HIT in CS patients**

Only one platelet count pattern strongly predicts for HIT post-CPB, namely a new platelet count fall (usually >50%) that begins between postoperative days 5 and 10 (9, 20). Although HIT is frequently considered in patients who develop early-onset and persisting thrombocytopenia post-CS (20), detection of antibodies is probably most often the result of “incidentally-detected” seroconversion, and the thrombocytopenia is most likely not caused by HIT (9). Rather, the low platelet count indicates severe morbidity with an increased risk of bleeding.

The 4Ts score for estimating the pretest probability of HIT, which was developed in mixed patient populations (21), improves the specificity of laboratory tests also in CS patients (22, 23). For example, the specificity of an anti-PF4/H immunoassay to predict a positive functional assay increased from 26% to 70% when interpreted together with an intermediate/high 4Ts score (21, 23).

**Management of CPB surgery**

In patients with acute or a history of HIT, elective surgery should be postponed until the patient tests negative for platelet-activating HIT antibodies, either by EIA or (in a patient whose EIA remains positive) in a washed platelet activation assay (serotonin release assay or heparin-induced platelet activation

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**Table 1: Frequency of anti-platelet factor 4/heparin (PF4/H) antibodies by enzyme-immunoassay (EIA), either polyclonal or individual Ig classes, in cardiac surgery patients before cardiopulmonary bypass (CPB) surgery and their association with patient outcomes.**

<table>
<thead>
<tr>
<th>Authors (year) (ref.)</th>
<th>Patient number</th>
<th>Frequency of anti-PF4/H antibodies by EIA</th>
<th>Association with patients outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer et al. (1997) (1)</td>
<td>111</td>
<td>19% IgGAM</td>
<td>No difference in thrombocytopenia and thromboembolic complications</td>
</tr>
<tr>
<td>Bennett-Guerrero et al. (2005) (7)</td>
<td>466</td>
<td>13% IgGAM</td>
<td>Longer hospital stay (12.9 ± 7.3 vs 11.9 ± 18.3 days; p = 0.284) in anti-PF4/H antibodies positive patients</td>
</tr>
<tr>
<td>Everett et al. (2007) (6)</td>
<td>299</td>
<td>4.3% IgGAM</td>
<td>No difference in thrombocytopenia and thromboembolic complications</td>
</tr>
<tr>
<td>Kress et al. (2007) (14)</td>
<td>1114</td>
<td>5.4% IgGAM</td>
<td>Longer mean hospital stay after surgery (14.0 vs 9.8 days, p = 0.05), higher risk for prolonged (&gt;96 h) mechanical ventilation (20.3% vs 9.2%, p = 0.02), higher risk for acute limb ischaemia (5.1% vs 0.9%, p = 0.03), renal complications (20.3% vs 10.5%, p = 0.03), and gastrointestinal complications (15.3% vs 5.9%, p = 0.01)</td>
</tr>
<tr>
<td>Mattioli et al. (2009) (15)</td>
<td>500</td>
<td>15.6% IgGAM</td>
<td>Significantly more thrombotic events in patients who developed antibodies after CPB surgery (57.7% vs 37.7%, p&lt;0.001)</td>
</tr>
<tr>
<td>Selleng et al. (2010) (5)</td>
<td>591</td>
<td>21.7% IgGAM, 7.4% IgG, 6.1% IgA, 13.4% IgM</td>
<td>No increased risk for thrombotic events and other adverse outcomes (non-thrombotic adverse events, length of in-hospital stay) in anti-PF4/H IgG, IgA and IgM positive patients; no increased risk for HIT in IgM positive patients, but increased risk for non-thrombotic adverse events in anti-PF4/H IgM positive patients</td>
</tr>
</tbody>
</table>

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Table 2: Frequency of anti-platelet factor 4/heparin (PF4/H) antibodies by enzyme-immunoassay (EIA), either polyspecific for immunoglobulin (Ig) GAM or separated Ig classes, in cardiac surgery patients after cardiopulmonary bypass (CPB) surgery without HIT and their association with patient outcomes. Only studies reporting adverse outcomes others than HIT are considered.

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Patient number</th>
<th>Frequency of anti-PF4/H antibodies by EIA</th>
<th>Association with patient outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer et al. (1997) (1)</td>
<td>111</td>
<td>19 % IgGAM</td>
<td>No difference with regard to thrombocytopenia or thromboembolic complications between antibody-positive and -negative patients</td>
</tr>
<tr>
<td>Kerendi et al. (2007) (18)</td>
<td>487 thrombocytopenic patients (platelets &lt;100 x10^9/l or platelet count drop&gt;50%)</td>
<td>23.2 % IgGAM</td>
<td>Higher incidence of postoperative infections, including sepsis (16.8 % vs 9.9 %, p&lt;0.05), pneumonia (46.9 % vs 23.3 %, p&lt;0.001), renal failure requiring haemodialysis (23.0 % vs 9.1 %, p&lt;0.001), acute limb ischaemia (15.9 % vs 4.3 %, p&lt;0.001), and higher 30-day mortality (24.8 % vs 15.2 %, P&lt;0.05) in thrombocytopenic patients testing positive for anti-PF4/H antibodies</td>
</tr>
<tr>
<td>Everett et al. (2007) (6)</td>
<td>277</td>
<td>22.4 % IgGAM</td>
<td>Six thromboembolic complications in antibody-positive and 9 in antibody-negative patients</td>
</tr>
<tr>
<td>Mattioli et al. (2009) (15)</td>
<td>500</td>
<td>26.2 % IgGAM</td>
<td>More thrombotic events (28.2 % vs 14.9 %, p&lt;0.01) and a higher incidence of the composite endpoint of death/myocardial infarction (14.5 % vs 7.8 %, p&lt;0.001) in antibody-positive patients</td>
</tr>
<tr>
<td>Mattioli et al. (2009) (17)</td>
<td>250</td>
<td>31.6 % IgGAM</td>
<td>Lower mean postoperative platelet count nadir (82 x10^9/l vs 105 x10^9/l, p&lt;0.001), more myocardial infarctions (25.3 % vs 10.5 %, p&lt;0.001), pulmonary embolism (20.2 % vs 5.8 %, p&lt;0.001) and strokes (12.6 % vs 5.8 %, p&lt;0.001) in antibody-positive patients</td>
</tr>
<tr>
<td>Gluckman et al. (2010) (19)</td>
<td>333 for IgGAM and 329 for IgG</td>
<td>52 % IgGAM and 37 % IgG</td>
<td>The composite endpoint of mortality, myocardial infarction, need for percutaneous coronary intervention, repeated coronary artery bypass graft (CABG) surgery, venous thromboembolism and stroke 6 weeks after CABG surgery did not differ between anti-PF4/H-IgGAM-positive and -negative patients (21 % vs 24 %; risk ratio=0.89, 95 % CI=0.59–1.33). This composite endpoint together with saphenous vein graft occlusion was comparable between the groups (45 % vs 44 %; risk ratio=1.03, 95 % CI=0.79–1.32).</td>
</tr>
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</table>

Table 3: Treatment protocol for bivalirudin anticoagulation during CPB.

<table>
<thead>
<tr>
<th>Bivalirudin dosing and monitoring before CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial i.v. bivalirudin bolus: 1.0 mg/kg body weight and initiate continuous i.v. infusion: 2.5 mg/kg/h</td>
</tr>
<tr>
<td>Bivalirudin added to pump circuit volume: 50 mg</td>
</tr>
<tr>
<td>Monitoring by ACT: A prolongation of ≥2.5-fold of baseline ACT level indicates adequate anticoagulation with bivalirudin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bivalirudin dosing and monitoring while on CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue i.v. infusion: ≥2.5 mg/kg/h</td>
</tr>
<tr>
<td>Frequency of bivalirudin level monitoring: Every 30 min by ACT</td>
</tr>
<tr>
<td>Prolongation of ≥2.5-fold of baseline ACT level: Keep bivalirudin infusion rate constant. Increase infusion rate only if ACT levels decrease below target or give repeated fractionated boluses of 0.25 mg/kg to maintain ACT in therapeutic range. Do not reduce infusion rate if ACT exceeds target.</td>
</tr>
</tbody>
</table>

**Heparin-induced thrombocytopenia**

For patients with acute HIT requiring urgent CS, several alternative anticoagulation strategies exist. These include using bivalirudin; the combined use of platelet inhibitors (i.e. epoprostenol, iloprost, or tirofiban) with UFH; and plasma exchange to permit UFH on CPB (16). The non-heparin anticoagulants, argatroban and danaparoid, cannot be recommended for CPB (see below).

**CPB surgery with bivalirudin**

In a randomised trial in non-HIT patients, complication rates (death, myocardial infarction, re-exploration, 24 h blood loss) were similar in the 101 patients who received bivalirudin compared to the 49 patients treated with UFH (30). The major drawback of bivalirudin is that it is cleaved by thrombin in stagnant blood. This pharmacological property requires special
surgical and perfusion considerations to avoid blood stagnation in the extracorporeal circuit and the operative site (31). Activated clotting time (ACT) is sufficient to monitor bivalirudin on CPB (Table 3). Bivalirudin has been recommended over other anticoagulation strategies in patients who cannot receive UFH on CPB (16).

**CPB with UFH and platelet inhibitors**

This strategy tries to utilise the familiar practice using UFH on CPB while the platelet inhibitors prevent HIT-related platelet activation. Case series in patients diagnosed with HIT could demonstrate reliable platelet inhibition using the prostaglandins epoprostenol (n=6) (32) and iloprost (n=22) (33) or the glycoprotein IIb/IIIa inhibitor tirofiban (n=47) (34) on CPB. Iloprost and epoprostenol cause vasodilatation and hypotension, and the half-life of tirofiban is prolonged in patients with impaired renal function, enhancing bleeding risk. These strategies seem to be justified in individual patients in whom bivalirudin is not applicable, e.g. in complex procedures or in institutions with minor experience using bivalirudin.

**Using UFH during CPB after pre-surgery plasmapheresis**

Therapeutic plasma exchange (plasmapheresis) aims to reduce the level of HIT antibodies and thereby decrease thrombotic risk. Two case reports described using plasma exchange either immediately before CPB with albumin and fresh frozen plasma as replacement fluids (35) or intraoperative plasma exchange against fresh frozen plasma (36). Voeller et al. described a series of plasmaphereses before CPB until the anti-PF4/H EIA became negative (37). In all patients, UFH was used for anticoagulation during CPB without any HIT-related complications or excessive bleeding. Unresolved questions remain the timing of plasmapheresis, the kind of replacement fluid, monitoring of HIT antibodies, and postoperative anticoagulation.

**Argatroban and danaparoid**

Case reports describe enhanced bleeding after stopping argatroban at the end of CPB (38, 39). Even more problematic was clot formation in the extracorporeal circuit while the ACT was still nearly 500 seconds (s) (38). Currently, argatroban is not recommended for anticoagulation during CPB surgery (16).

A review that analysed 1478 clinical outcomes of patients treated with danaparoid included 130 patients receiving danaparoid on CPB (40). These patients received 125 units (U) danaparoid/kg intravenously (i.v.) before CPB, and 3 U/ml were added to the priming fluid. Maintaining dose on CPB was 7 U/kg/hour (h) until 45 minutes (min) prior to bypass disconnection. The long plasma half-life of danaparoid (18 h) and the lack of a point-of-care test for monitoring during surgery presumably resulted in the increased bleeding risk with major bleeding events in 42%. Thus, danaparoid can only be recommended in the absence of an alternative or if an antidote becomes available (see section HIT in the ICU).

**Off-pump coronary artery bypass grafting (OPCAB)**

Danaparoid, argatroban and bivalirudin have been used in OPCAB. Increased transfusion requirement with danaparoid (41) and insufficient anticoagulation with argatroban (42) limit the use of these agents. In contrast, bivalirudin was used successfully in OPCAB (Table 4) (43, 44).

**Percutaneous cardiovascular interventions**

Percutaneous cardiovascular interventions, e.g. transcatheter aortic valve implantation (TAVI) or MitraClip procedure, have replaced CPB surgery in selected patients. Bivalirudin has demonstrated to show similar safety and efficacy as UFH in TAVI (45, 46) and should also be applicable for MitraClip intervention (47). Doses have been adopted from the large percutaneous intervention studies using an intravenous bolus of 0.75 mg/kg followed by continuous infusion of 1.75 mg/kg/h (48).

**Ventricular assist devices**

Ventricular assist devices (VAD) are mechanical pumps supporting impaired cardiac function. Blood exposure to artificial surfaces provokes a prothrombotic situation that requires systemic therapeutic-dose anticoagulation to prevent pump thrombosis. UFH aiming at 1.5– to 2.5-fold activated partial thromboplastin time (aPTT) prolongation is the standard anticoagulation management in the first postoperative week, subsequently replaced by vitamin K antagonists (VKA) plus antipla-telet agents (49).

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**Table 4: Treatment protocol for bivalirudin anticoagulation in OPCAB surgery.**

<table>
<thead>
<tr>
<th>Dosing of bivalirudin</th>
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</thead>
<tbody>
<tr>
<td>Bolus: 0.75 mg/kg followed by continuous infusion of: 1.75 mg/kg/h (stop infusion approx. 20 min before end of grafting); ACT &gt; 300 s</td>
<td></td>
</tr>
</tbody>
</table>

**Considerations of graft handling**

- Assessments of grafts for patency and leakage should be performed. Grafts should be flushed with saline. Stasis of the blood stream is associated with potential risk for thrombus formation in the graft and has to be strictly avoided.

- ACT, activated clotting time; CPB, cardiopulmonary bypass; OPCAB, off-pump coronary artery bypass.
Epidemiology and clinical presentation of HIT in VAD patients

Anti-PF4/H antibodies have been found in more than 50% of patients before VAD implantation and in almost three of four patients in the postoperative period (50). HIT has been seen in 4.2% before and >10% after VAD implantation (50, 51) although the risk of overdiagnosing HIT in VAD patients is high (52). VAD patients with HIT had a higher risk for thromboembolic complications, especially thromboembolic stroke (odds ratio=3.8; p=0.043) (53), but not for pump thrombosis (50).

Non-heparin anticoagulation

Due to the high number of VAD patients with suspected or confirmed HIT, UFH has to be replaced in a considerable number of patients. Alternative non-heparin anticoagulation strategies have been developed (54), primarily using argatroban and bivalirudin.

Argatroban has successfully been used after VAD implantation (0.02–0.4 µg/kg/min as starting dose, followed by 0.02–1.5 µg/kg/min as maintaining dose achieving >1.5-fold aPTT prolongation, but <100 s) (54, 55). With a frequency of about 20% each, bleeding as well as thromboembolic events were common (54, 55), but not more frequent compared to UFH in non-HIT patients (55). Experience with argatroban during VAD implantation derives from a case series of seven patients in whom preoperative argatroban anticoagulation was continued for CPB (56). The first patient was treated with a target aPTT of 50–60 s during surgery and suffered from severe intraoperative cardiac and device thrombosis. Target aPTT was therefore increased to 70–80 s in the remaining six patients allowing successful surgical procedure without any clotting. However four patients needed re-exploration due to bleeding and three patients died (survival rate 4/7 patients=57.1%). These experiences suggest that argatroban is feasible before and after VAD implantation, but not during surgery.

The best data on bivalirudin in VAD patients provides a case series of 12 patients in whom bivalirudin was used as primary anticoagulant after VAD implantation (57). The starting dose was 0.025 mg/kg/h following a mean dose of 0.040 ± 0.026 mg/kg/h targeting an aPTT of 45–60 s. No thromboembolic events and only two minor bleedings occurred. Regarding the anticoagulation management during CPB surgery, special surgical techniques (58, 59) aim to reduce blood stagnation, thereby allowing bivalirudin during VAD implantation using the protocol given in Table 3.

Intensive care unit patients

Frequency, diagnosis and “prophylaxis” of HIT

HIT is rare in ICU patients occurring in ~0.5% of patients (60, 61). As thrombocytopenia is seen in almost every second critically ill patient (62), and anti-PF4/H antibodies are also frequent in ICU patients (2, 63), the diagnostic dilemma is comparable to that in CS patients. To solve this, the 4Ts score has been tested in ICU patients for its ability to rule out HIT in patients with a low pretest probability (64). Of the 474 eligible patients, 407 (85.9%) had a 4Ts score of ≤3, but six of them tested positive in a functional assay. However, the 4Ts score in these six patients was falsely low, as the adjudicators did not have the information about pre-study enrolment heparin exposure. The 4th criterion „oTher causes of thrombocytopenia” generated the most disagreement. A modified 4Ts score omitting this criterion was assessed, but did not improve pretest probability (65). An observational study suggests that specificity of laboratory tests for HIT antibodies increases without losing sensitivity when they are limited to patients presenting with a significant platelet count fall after day 4 of ICU admission (2) (Figure 1).

The use of low-molecular-weight heparin (LMWH) has proven to be associated with a lower risk of HIT in several patient populations (10, 66). ICU patients treated with the LMWH, dalteparin,
for thromboprophylaxis also had a lower risk of developing HIT versus patients receiving UFH (hazard ratio=0.27; 95 % confidence interval=0.08–0.98; p=0.046) (67).

**General measures in the management of HIT**

When HIT is strongly suspected or confirmed, heparin has to be substituted by a non-heparin anticoagulant, usually given in therapeutic dose (16). In patients with moderate suspicion of HIT, intensity of anticoagulation should be adapted to the bleeding risk. Prophylactic dose non-heparin anticoagulation may be appropriate in selected ICU patients until the results of the HIT testing are available. The definite diagnosis of HIT should clearly be indicated in the medical record to avoid any accidental heparin administration (68). As HIT is a prothrombotic disease, plateau transfusion should be restricted to thrombocytopenic patients with relevant bleeding (16). Finally, ultrasound should be performed of the lower limb and limbs with central lines, as deep-vein thrombosis is common in HIT and has impact on intensity and duration of anticoagulation (68, 69).

**Alternative anticoagulation in the ICU**

The choice of the alternative anticoagulant requires careful consideration of liver and renal function.

Argatroban has a short half-life that is not affected by renal function (70). The short half-life can result in insufficient anticoagulation when drug administration is (accidentally) interrupted. A major issue is aPTT-confounding by low fibrinogen or prothrombin levels, which leads to a falsely high aPTT during argatroban administration. Further, several underlying diseases which are frequent in ICU patients, such as disseminated intravascular coagulation, liver failure, and consumption of coagulation factors XI and XII on extracorporeal circuits, cause aPTT prolongation despite relatively low argatroban plasma levels, thereby provoking inappropriate argatroban dose reduction. Probably, modified ecarin-based assays performed with fibrinogen in excess (71) or plasma-diluted thrombin time (72) may help to overcome this problems. Importantly, argatroban’s half-life depends on liver function, which requires dose adjustment.

Bivalirudin is frequently used in Switzerland where it had been the only available alternative anticoagulant, but no prospective studies are available in ICU patients. Liver and renal functions have only a moderate effect on its half-life. Bivalirudin was used in combination with alteplase to perform catheter-directed lysis over 36 h of a lower limb thrombus in an ICU patient with HIT (73).

The indirect anti-factor Xa (aFXa) inhibitors danaparoid (74) and fondaparinux (75) provide the major advantage of reliable anticoagulation monitoring by aFXa-activity (68) (using standard curves calibrated with the drug of interest) which helps to detect drug overdose in case of bleeding. For both drugs prophylactic-dose regimens are established, which can be used in patients at risk for bleeding while awaiting laboratory HIT test results. The major disadvantages of both drugs are their long half-lives (25 h and 18 h, respectively) that is further prolonged in patients with renal impairment requiring dose reductions by at least 30 %.

Recently, preliminary data became available regarding an antidote for FXa inhibitors, andexanet alpha (76). Its pharmacological properties could provide an opportunity to reverse danaparoid (77), which would open new options for use of danaparoid in ICU patients.

**Extracorporeal circuits**

**Continuous renal replacement therapy (CRRT)**

CRRT requires anticoagulation to prevent clotting of the extracorporeal circuit. Non-heparin anticoagulation can be performed by systemic therapeutic-dose anticoagulation using bivalirudin, argatroban, or danaparoid, or regional anticoagulation with citrate.

Regional citrate anticoagulation is performed by infusing citrate into the haemofilter, thereby binding calcium and inhibiting clot formation in the filter. Longer filter survival times, lower costs (78) and presumably a lower bleeding risk favour citrate over heparin. Regional citrate anticoagulation has therefore the potential to become the standard in CRRT (79), lowering the need for UFH in ICU patients. Further, it is an option in patients with a history of HIT or after the acute phase of HIT. However, acute HIT requires additional systemic non-heparin anticoagulation to prevent HIT-associated thromboembolic complications.

Bivalirudin at doses of 0.03–0.04 mg/kg/h has proven to be sufficient to ensure anticoagulation for CRRT in ICU patients (80). One prospective randomised double-blind study has compared this regimen to UFH in non-HIT patients by giving bivalirudin 2 mg/h i. v. vs 400U/h UFH without initial bolus (81). Haemofilter patency was significantly longer with bivalirudin (29.6 ± 20.7h vs 16.5 ± 13.6h, p=0.045). Bleeding (one event) as well as thrombosis (one event) occurred only in patients receiving heparin (22 filters), but not with bivalirudin (18 filters). In patients with liver impairment, bivalirudin has likely a lower risk to accumulate than argatroban.

Argatroban has also been used successfully for CRRT in the ICU. After a bolus of 100 µg/kg, argatroban is given continuously targeting a 1.5–3.0-fold aPTT prolongation. The argatroban required dose depends on the severity of illness and ranges from 0.1–1.5 µg/kg/min (average rate 0.7 µg/kg/min) (82). A retrospective single-centre study that assessed the outcome in HIT patients treated either with bivalirudin, argatroban or lepirudin (no longer available) for continuous or intermittent RRT found no difference in the triple composite endpoint of thrombosis, haemorrhage and in-hospital mortality (83).

Danaparoid was used during CRRT in patients with suspected HIT (n=5) with a loading dose of 3,500 U followed by continuous infusion of 100 U/h without bleeding or thromboembolic events (84). In patients with a low to moderate bleeding risk, the long half-life of danaparoid provides a stable level of anticoagulation.

Platelet inhibiting agents, like epoprostenol, have been used in combination with UFH or alone to ensure anticoagulation in CRRT. When used without heparin, patients suffered more
frequently from arterial hypotension (85). In a prospective observational study comparing citrate to epoprostenol combined with heparin, citrate provided longer filter survival times and lower costs. Further, four of 17 patients of the epoprostenol group had to be switched to citrate due to thrombocytopenia (86). Because of these limitations and the unresolved problem of systemic anticoagulation, epoprostenol cannot be recommended for CRRT in patients with acute HIT.

Extracorporeal membrane oxygenation (ECMO)

ECMO provides circulatory and/or pulmonary support in patients with cardiac or respiratory failure. Established anticoagulation strategies include therapeutic dose UFH, bivalirudin and argatroban (87). Danaparoid was anecdotally used for ECMO at a dose of 400 U/h targeting an aFXa level of 0.6–0.8 U/ml (88).

The best data supporting the use of bivalirudin in ECMO patients derive from a case-control study (89). The median bivalirudin dose needed to achieve an aPTT of 45–60 s was 0.041 ± 0.028–0.05 mg/kg/h. In patients treated with bivalirudin for ECMO, any outcome parameters such as bleeding, thromboembolic events, time of ECMO, mortality, and the stability of anticoagulation were similar compared to UFH.

A case series of 9 ECMO patients being anticoagulated with argatroban demonstrated that a dose of 0.2 µg/kg/min is sufficient to increase the aPTT to 50–60 s, which is lower than recommended by the manufacturer (90). Considering the decreased dose requirements, argatroban was feasible and effective, permitting ECMO in patients with suspected HIT.

Conclusions

Non-heparin anticoagulation strategies have been used successfully in CS patients and those treated in the ICU. These anticoagulants cannot readily compete with UFH, an agent with pharmacokinetics independent of organ function, easily monitored, and rapidly antagonised with protamine. Laboratory assays for HIT antibodies can rule out HIT, but the diagnosis of HIT requires a stepwise approach with careful consideration of the clinical picture. The use of LMWH for thrombosis prophylaxis and the use of regional citrate anticoagulation for RRT are easy to perform and may help to lower the risk of HIT.

Conflicts of interest

None declared.

References