Review Article

Results of a consensus meeting on the use of argatroban in patients with heparin-induced thrombocytopenia requiring antithrombotic therapy – An European Perspective

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Abstract

Argatroban has been introduced as an alternative parenteral anticoagulant for HIT-patients in several European countries in 2005. In 2009 a panel of experts discussed their clinical experience with argatroban balancing risks and benefits of argatroban treatment in managing the highly procoagulant status of HIT-patients. This article summarizes the main conclusions of this round table discussion. An ongoing issue is the appropriate dosing of argatroban in special patient groups. Therefore, dosing recommendations for different HIT-patient groups (ICU patients; non-ICU patients, paediatric patients, and for patients undergoing renal replacement therapies) are summarized in this consensus statement. Because of the strong correlation between argatroban dosing requirements and scores used to characterize the severity of illness (APACHE; SAPS, SOFA) suitable dosing nomograms are given.

This consensus statement contributes to clinically relevant information on the appropriate use and monitoring of argatroban based on the current literature, and provides additional information from clinical experience. As the two other approved drugs for HIT, danaparoid and lepirudin are either currently not available due to manufacturing problems (danaparoid) or will be withdrawn from the market in 2012 (lepirudin), this report should guide physicians who have limited experience with argatroban how to use this drug safely in patients with HIT.

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Introduction

Argatroban is a direct thrombin inhibitor (DTI) that has been approved in USA, Canada, Japan, and several European countries for anticoagulation in patients with immune-mediated heparin-induced thrombocytopenia type II (HIT) who require antithrombotic therapy. In HIT, antibodies of the immunoglobulin G class against platelet factor 4 (PF4)/heparin complexes [1–3] induce intravascular platelet activation and consequent thrombin generation [4–7], resulting in an enhanced risk for venous and/or arterial thrombosis [8–10]. HIT requires immediate change to an alternative anticoagulant to control the thrombin burst induced by HIT [11–13]. However, the majority of patients with suspected HIT are critically ill patients [14] in whom either the underlying disease or preceding interventions may simultaneously impose a bleeding risk. In addition to their severe underlying disease they often have several comorbidities, most frequently renal impairment [15]. The comorbidities enhance the risk for hemorrhagic complications, especially if the comorbidities alter the pharmacokinetics of alternative anticoagulants. For a decision on the timely switch from heparin treatment to alternative anticoagulation, the physician needs to consider the complexity of this procoagulant state, with a high risk for new thrombotic complications, and on the other hand, the problem of a definite HIT diagnosis and the risk of adverse events induced by alternative, non-heparin anticoagulation. Moreover any decision on resource allocation in modern health care systems has to take into account the precept of cost-effectiveness.

HIT is a common-rare disease, i.e. the incidence is too low to allow well-designed prospective randomized trials but it is frequent enough to be a clinically relevant problem.

This challenging background motivated argatroban users and experts in hemostasis and HIT from Austria, Denmark, Finland, Germany, Italy, The Netherlands and Norway to exchange their experiences on the treatment of patients with HIT with a special focus on argatroban. This meeting took place in Munich/Germany in September 2009. During the meeting the different participants exchanged their clinical experience when using argatroban as an alternative coagulant in different patient groups (e.g. post-surgical patients, cardiac-surgery patients, intensive care unit patients) under the conditions of their local health care systems. Each expert covered a one of the topics regarding the use of argatroban, presenting the evidence from the literature and the experiences made in his center. The presentation was followed by a round table discussion on the main conclusions. When all participants agreed, the conclusion was accepted and included into this manuscript. In case of disagreement the issue was discussed until a consensus on the wording was reached among the panel members.

The main consensus points of this expert meeting were summarized and then the written statements were refined by the participating experts. The final common expert opinion obtained informally is presented in this article with the aim of contributing to the clinically relevant information on the appropriate use of argatroban present in the literature, and also to provide practical information resulting from the clinical management of these patients on a daily basis, beyond the data obtained from clinical studies. According to the strength of recommendation taxonomy (SORT) [16] of evidence of the recommendations given in this article have all to be graded as 2 C.

Argatroban

Argatroban binds highly selective and reversible to the active catalytic site of thrombin without needing any co-factors. Argatroban is well tolerated; the major adverse effect is – as it is with all anticoagulant drugs – bleeding. Clinical trials on efficacy and safety of argatroban in patients with HIT or HIT with thrombomembolic complications (HITTS) showed that in ≥83% of argatroban treated patients adequate anticoagulation levels were reached within 3–4.5 hours after starting infusion. Argatroban is metabolized hepatically and excreted mainly with the feces (65.4%). Pharmacokinetic of argatroban does not depend on renal function. Other than all other alternative anticoagulants, argatroban can be used without dose adjustment in patients with renal impairment.

A prospective clinical trial [17] found that major bleedings (defined as overtly associated with a hemoglobin decrease ≥2 g/dl that led to a transfusion of ≥2 units, or that were intracranial, retroperitoneal, or into a major prosthetic joint), most of them gastrointestinal, occurred in 7.1% (19 of 269 patients) of the patients treated with 2 μg/kg x min of argatroban (median dose [range] 1.9 [0.2–9.7] mg/kg x min for 5.6 [0.1–61] days). Fatal outcome due to bleeding was observed in 0.7% (2 of 269) of patients which were treated with multiple anticoagulants and thrombolytic therapy. To minimize bleeding risk during argatroban therapy the aPTT should not exceed <90 seconds.

Beside argatroban, two other drugs are approved for treatment of patients with HIT, danaparoid and lepirudin. Danaparoid is not available due to manufacturing problems since several years in many countries and lepirudin will be retrieved from the market by the manufacturer in April 2012. We therefore do not discuss these options in detail. The interested reader is referred to summaries of both drugs in the ACCP guidelines [11] and in a text book on heparin-induced thrombocytopenia [18].

A major limitation of argatroban is that it can only be given by continuous i.v. infusion. This causes problems in patients after the very acute phase of HIT who should be mobilized. There are evolving data that fondaparinux might become an option for alternative anticoagulation in these patients [19].

Patients at risk of HIT and HIT diagnosis

The mean incidence of HIT varies largely between patient groups. The highest incidence of HIT (~7–10%) has been observed in patients with a cardiac assist device receiving unfractionated heparin (UFH) [20]. The second most frequent incidence of HIT was observed in patients receiving thrombosis prophylaxis with UFH after major orthopedic joint replacement surgery (3–5%) [21].

There is increasing evidence that there are several risk factors for HIT. Females have a higher risk of developing HIT than males [22], and patients undergoing major surgery have a higher risk as compared to patients undergoing minor surgery or medical or obstetrical patients [23–25]. Best documented is the type of heparin as a risk factor. With low-molecular-weight heparin (LMWH) the risk for HIT is only ~10% of the risk associated with UFH after major surgery [22, 26–28], and the risk is also likely to be reduced in medical patients [23–25]. In medical patients, those with stroke and cancer are probably the patients with the highest risk of developing HIT [29, 30].
In order to differentiate whether thrombocytopenia is caused by HIT or by other conditions, an algorithm based on the typical features of HIT can be helpful to determine the probability of HIT, especially for the non-specialist. We suggest to assess each patient treated with heparin within the last 4 weeks, within 12 hours after the start of heparin, and all other patients from day 5 to 14 every alternate day, for a decrease in platelet count by $\geq 50\%$ from the highest value after start of heparin, or a new thrombosis. If one or both of these two signs is or are observed, we suggest determining the pretest probability of HIT by using the 4 T score [31] (Fig. 1). Platelet count monitoring in patients receiving heparin is a controversially discussed issue. Ideally all patients should be monitored for a platelet count decrease, which, however, is not practical, especially in outpatient settings. As HIT is especially frequent in patients receiving unfractionated heparin after major surgery [32], we recommend to monitor platelet counts in this group whenever possible.

HIT usually features a platelet count fall $>50\%$ (from the highest value after start of heparin treatment) [33, 34], most often to a nadir between $50 - 80 \times 10^9/L$ [35] and/or a new thrombosis, typically occurring 5–14 hours after the start of prophylactic or therapeutic doses of heparin. Timing of onset, the moderate nature of thrombocytopenia, and the common concurrence of thrombosis, are very important factors to differentiate HIT from other causes of thrombocytopenia. In about one third of HIT patients thrombotic events occur even before thrombocytopenia is clinically detected [36-38]. Patients with early-onset thrombocytopenia or a platelet count $<20 \times 10^9/L$ usually do not have HIT [38]. Thromboembolic complications predominantly affect the venous system. Other rare complications include skin necrosis [39, 40], adrenal hemorrhagic necrosis (most often seen in ICU HIT patients, and caused by adrenal vein thrombosis) [9, 36] or post-intravenous heparin bolus anaphylactoid reactions [41]. A platelet count fall within the first 3 days after the start of heparin ($=\text{rapid onset HIT}$) can be observed in preimmunized patients who had received heparin usually within the past 30 days [42, 43]. If the 4 T score is below 4, the underlying cause for thrombocytopenia is most probably not HIT, and there is no need for further tests. If the 4Ts score is 4 or higher, HIT should be considered as a potential cause of thrombocytopenia.

Diagnosis of HIT is especially problematic in critically ill patients, as the two leading symptoms of HIT – thrombocytopenia and thrombosis – are not specific for HIT. HIT is frequently overdiagnosed in patients with comorbidities causing thrombocytopenia [44-46]. The absence of antibodies against PF4/heparin complexes can rule out HIT by approx. 98-99\% (high negative predictive value) but the presence of anti-PF4/heparin antibodies alone cannot confirm a diagnosis [14, 47, 48]. PF4/heparin antibodies are much more frequently observed than clinical HIT [38, 49] and diagnosis should not only be based on a positive antigen test result (PF4/heparin enzyme linked immunosorbent assay [ELISA] or particle gel immunoassay). More specific for identifying clinically relevant antibodies are functional assays using washed platelets, like the serotonin release assay [50, 51] or the heparin-induced platelet activation assay [52]. Whole blood or PRP based assays can also confirm the diagnosis but these assays have a low sensitivity and false negative results may occur [47, 53, 54].

To prevent new thrombosis, non-heparin anticoagulant therapy is required in HIT. Stopping heparin alone is insufficient. When there is a very high clinical suspicion of HIT, alternative anticoagulation should be started immediately and laboratory diagnosis of HIT can then be used to confirm or rule out the diagnosis in retrospect [11]. Three drugs are approved for anticoagulation in HIT: two direct thrombin inhibitors (DTIs), argatroban and lepirudin, and a heparinoid, danaparoid (factor Xa inhibitor), but only argatroban is currently widely available. All alternative anticoagulants confer significant risks for major bleeding (0.8-1.25% per treatment day) and no anticoagulation is available for any of them [11].

Vitamin K antagonists (VKA) must not be given in acute HIT [11]. They can induce venous limb gangrene in the extreme hypercoagulable milieu of HIT because of VKA-induced protein C depletion [11]. In case of low to moderate suspicion of HIT, management depends on the availability and turnaround time of laboratory tests for PF4/heparin antibodies. As a general rule, the higher the clinical suspicion

![Fig. 1. Recommended algorithm for the decision on the timely switch from heparin treatment to alternative anticoagulation for HIT. Note that the treatment decision is based primarily on clinical factors. In patients who receive heparin in therapeutic dose, the platelet count value can be obtained from the blood sample needed for aPTT monitoring. In patients receiving UFH for thrombosis prophylaxis after major surgery, platelet counts should be monitored every alternate day between day 4 and 14. In all other patients special attention should be given to platelet counts obtained for other reasons, but no additional blood counts for monitoring HIT are required. Abbreviation: HIT, heparin-induced thrombocytopenia type II. See text for further details.](image-url)
for HIT, the greater the necessity to change the anticoagulation regimen to an alternative non-heparin anticoagulant. The following part of this report focuses on the use of argatroban.

Patients most eligible for argatroban treatment

Argatroban is metabolized in the liver [55, 56] and is so far the only alternative anticoagulant to heparin that shows pharmacokinetic properties independent of renal function. Therefore, the risk of accumulation is negligible in patients with developing renal insufficiency, a feature very often present in patients suspected to have HIT. Argatroban shows a fast onset of action and has a short elimination half-life of 52 ± 16 min [57]. Argatroban is a small molecule with almost no immunogenicity [58] that is administered only intravenously (i.v.). As with all other anticoagulants, except standard heparin, there is no antidote available. Argatroban, however, is metabolized by the liver [50, 51]. In patients with impaired liver function (Child-Pugh Score 7 – 11), or impaired liver perfusion (e.g. in case of cardiac insufficiency), the dose of argatroban has to be adjusted [59, 60], and it should not be given in patients with severe hepatic failure.

While argatroban is a highly efficient direct thrombin inhibitor [61, 62], argatroban specifically meets the needs of severely ill, immobile patients with several i.v. lines, who suffer from renal insufficiency and who need a short-acting anticoagulant that is easily to be monitored and controlled. These are the characteristics of patients typically treated in intensive care units (ICU). This description also includes patients at risk of invasive diagnostic or therapeutic procedures.

Monitoring of argatroban

Argatroban is routinely monitored by the activated partial thromboplastin time (aPTT). In general the target aPTT range is 1.5 to 3.0 times baseline [63, 64]. Since the aPTT tends to show a ceiling effect [65], the ecarin clotting time (ECT) or the ecarin chromogenic assay (ECA-T) – where available – may be considered preferable tests in patients who require very high dose treatment (above the range when the aPTT dose–response curve flattens). In these assays the dose response curve exhibits linearity over a wider dose range [66], although the target range has not been determined. Commercially available aPTT kits exhibit different sensitivities to argatroban. The simple adoption of standard values from another aPTT test system to the one used locally may lead to an underestimation or overestimation of the aPTT and consequent overdosing/underdosing of argatroban. Therefore we suggest that each laboratory generates its own dose response calibration curve, because the variation of tests depends on both the test kit as well as the laboratory device itself. As argatroban binds specifically to thrombin, a standard curve can be generated by spiking normal plasma ex vivo.

ICU patients are often deficient in prothrombin, resulting in falsely prolonged aPTTs or ECTs during DTI treatment. In such cases it would be advisable to employ the thrombin time (TT) method which is independent of the prothrombin level. After creating a calibration curve of the specific TT in the laboratory with a dilution series of argatroban in normal plasma and correlating it with the aPTT, the determination of the patient’s TT would reveal a “corrected” aPTT value. Otherwise, the ECA-T allows the drug concentration to be precisely assessed by providing a linear dose response curve over a wide concentration range of argatroban [66]. The ECA-T is currently adopted for as one of the parameters where available – may be considered preferable tests in patients who require very high dose treatment (above the range when the aPTT dose–response curve flattens). In these assays the dose response curve exhibits linearity over a wider dose range [66], although the target range has not been determined. Commercially available aPTT kits exhibit different sensitivities to argatroban. The simple adoption of standard values from another aPTT test system to the one used locally may lead to an underestimation or overestimation of the aPTT and consequent overdosing/underdosing of argatroban. Therefore we suggest that each laboratory generates its own dose response calibration curve, because the variation of tests depends on both the test kit as well as the laboratory device itself. As argatroban binds specifically to thrombin, a standard curve can be generated by spiking normal plasma ex vivo.

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Dosing schedules

The generally recommended dose of argatroban is 2.0 μg/kg•min [63, 64] (Table 1). However, based upon the experience gained over the past years, dosing schedules have been optimized for specific patient groups, particularly with regard to the ICU setting [67]. The basic finding is that in ICU patients with a suspicion of HIT, significantly lower argatroban doses than previously recommended, are sufficient for a prolongation of the aPTT into the target range indicating effective anticoagulation [68]. In patients with no symptoms for impaired liver function/perfusion we suggest to start with 1.0 μg/kg•min argatroban at an infusion rate high enough to compensate for the time the drug needs to get from the infusion pump or bag into the patient, if lines are used which are not prefiltered with argatroban containing fluid. If the thrombotic event is life-threatening, we suggest to consider 2.0 μg/kg•min argatroban, while taking care of the individual bleeding risk.

Recently, increasingly published experience lead to an update of the summary of product characteristics (SmPC) of argatroban, resulting in dose recommendations for critically ill patients of 0.5 μg/kg•min. In an ICU setting we consider in a patient with acute new thrombosis that the risk of further new thrombosis is more serious than the risk of bleeding. In patients with increased bleeding risk, the treatment should be started at a lower dose and titrated upwards until the target aPTT range is reached. In any case, the aPTT should be monitored every 2 hours and the dose adjusted accordingly until a steady state is reached. Then monitoring every 8 – 12 hours is sufficient.

In ICU patients with a suspicion of HIT but without an acute thrombotic complication we suggest to start with 0.5 μg/kg•min argatroban, to determine the aPTT every 2 hours and adjust the dose until the target aPTT is attained, while taking care of the individual bleeding risk. In order to minimize the time of titration we encourage the calculation of the appropriate argatroban dose from the sequential organ failure assessment (SOFA)-II score (Fig. 2A), the acute physiology and chronic health evaluation (APACHE)-II score (Fig. 2B) or the simplified acute physiology score (SAPS)-II (Fig. 2C), or from a critically ill / hepatic nomogram [69,70,71]. If for intervention-related procedures or any other reason the administration of argatroban is interrupted, most of its efficacy will be lost after 2 – 4 hours in a patient with normal metabolism. This allows invasive interventions but also puts the patient at an increased risk for thrombosis, if argatroban is stopped e.g. for CT-scan investigation in the radiology department.

In non-ICU patients with a suspicion of HIT, with moderate to normal renal function and no evidence of hepatic impairment, we suggest to start with the approved dose of 2.0 μg/kg•min argatroban and to determine the aPTT every 2 – 4 hours. Note that this will be the minority of patients.

For patients requiring renal replacement therapy (RRT) there is limited data available on argatroban management. In patients on argatroban anticoagulation who are already in a steady-state, RRT therapy can be initiated simply by continuing the infusion without any initial adjustment: a bolus dose is not required. When argatroban treatment is started simultaneously with RRT we suggest to start with a bolus of 100 μg/kg argatroban and subsequent continuous infusion of 0.5 μg/kg•min argatroban for continuous RRT [70, 72], and with a bolus of 250 μg/kg argatroban and subsequent continuous infusion of 2.0 μg/kg•min argatroban for intermittent dialysis [73]. The maintenance infusion should be stopped one hour before the end of the haemodialysis procedure.

In patients undergoing invasive procedures there is little data available on peri-operative argatroban management [74, 75]. We suggest to stop argatroban administration in case of surgical procedures with a very high bleeding risk, such as laparotomy, 3 – 4 hours before the intervention and in the case of minor interventions 1 – 2 hours before the intervention controlling anticoagulation by aPTT before and during the intervention. For intravenous catheters and percutaneous tracheotomy we suggest continuing argatroban administration. In patients with liver impairment the half-life of argatroban can be substantially prolonged and the aPTT must be controlled before the intervention. In case of prolonged aPTT the intervention should be postponed until the aPTT reaches the upper limit of the normal range.

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Table 1
Recommendations for Argatroban Dosing. There is no dose adjustment required for patients with renal insufficiency or renal failure. Argatroban is contraindicated in patients with severe hepatic failure. In any case the individual bleeding risk has to be considered. (a) The dose should be adjusted according to SOFA-II score, APACHE-II score or SAPS-II (Fig. 2) or to a critically ill/hepatic nomogram. (b) ACT should be checked 5 to 10 minutes after the bolus dose is completed. (c) When the patient is already being treated with argatroban, there is no bolus required. (d) The infusion should be stopped one hour before the end of the haemodialysis procedure. Abbreviations: ACT, activated clotting time; APACHE, acute physiology and chronic health evaluation; aPTT, activated partial thrombin time; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; TE, thrombotic event. See text for further details.

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Initial Dose [μg/kg × min]</th>
<th>Bolus [μg/kg]</th>
<th>Monitoring Parameter and Frequency</th>
<th>Target Range to be Achieved by Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with HIT or Suspicion of HIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive Care Unit [i.e. Critically Ill Patients, Postoperative Cardiac Surgery] with acute life-threatening TE</td>
<td>2.0</td>
<td>-</td>
<td>aPTT two hours after every dose</td>
<td>aPTT 1.5-3.0 times baseline not exceeding 100 seconds</td>
</tr>
<tr>
<td>Patients, Postoperative with acute non-life-threatening TE</td>
<td>1.0</td>
<td>-</td>
<td>adjustment or at least once daily</td>
<td></td>
</tr>
<tr>
<td>Cardiac Surgery without TE</td>
<td>0.5 (a)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Intensive Care Unit without hepatic impairment</td>
<td>2.0</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with hepatic impairment</td>
<td>0.5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric without hepatic impairment</td>
<td>0.75</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with hepatic impairment</td>
<td>0.2</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Replacement Therapy (RRT)</td>
<td></td>
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<tr>
<td>Continuous RRT</td>
<td>0.5 (a)</td>
<td>100 (c)</td>
<td>aPTT</td>
<td>aPTT s. above</td>
</tr>
<tr>
<td>Intermittent RRT (Out Patients)</td>
<td>2.0</td>
<td>250</td>
<td>ACT</td>
<td>ACT 170-230 s (d)</td>
</tr>
<tr>
<td>Percutaneous Coronary Intervention (PCI)</td>
<td>25.0</td>
<td>350</td>
<td>ACT (b)</td>
<td>ACT 300-450 s</td>
</tr>
</tbody>
</table>

A
Argatroban infusion rate [μg/kg × min] = 2.18 - 0.09 x SOFA
Regression Analysis (SOFA-Score)

B
Argatroban infusion rate [μg/kg × min] = 2.15 - 0.06 x APACHE II
Regression Analysis (APACHE-II-Score)

Fig. 2. Dose nomograms for argatroban based on SOFA-II (3A), APACHE-II (3B), and SAPS-II (3C) scores.
Whenever possible, surgery should be avoided in the setting of acute HIT because of the very high risk of thrombosis and strong indication for uninterrupted anticoagulation.

**Argatroban in pediatric patients**

Several case reports and a chart review [76] indicate that argatroban can be used safely in children. In a review [77] 34 children treated with argatroban were identified between one week and 16 years of age. All patients received a continuous i.v. infusion of argatroban, titrated to achieve a target aPTT. The aPTT-adjusted doses ranged from 0.1 to 12 μg/kg x min. Four patients also received an initial argatroban bolus of 75 to 200 μg/kg. Bleeding occurred in three patients while on argatroban.

[78] performed an open-label, safety, efficacy, and pharmacokinetic study in 18 severely ill pediatric patients between 1.6 weeks and 16 years of age. They conclude that for continuous anticoagulation, argatroban 0.75 μg/kg x min, adjusted by aPTT, should be used in children (in case of hepatic impairment 0.2 μg/kg x min). In neonates [79-82] an argatroban bolus of 200 – 250 μg/kg has been reported followed by a continuous infusion rate of 7.5 – 10 μg/kg x min. Of note, this dose is much higher than the 1.0 – 2.0 μg/kg x min recommended in adults. In a newborn, argatroban was used for anticoagulation during extracorporeal membrane oxygenation (ECMO). After an initial bolus of 200 μg/kg, a continuous infusion at a rate of 3.0 – 7.5 μg/kg x min was started. During use of a ventricular assist device (VAD), safe anticoagulation with argatroban could be achieved in this infant with an infusion rate of 0.005 - 1.8 μg/kg x min. [83] achieved the target aPTT using 1–2 μg/kg x min in a 17-month-old boy requiring ECMO and hemofiltration, while [84] used 0.1 – 1.0 mg/kg x min in two term infants and a 1-year old girl, who required extracorporeal life support.

The literature reviewed by [77] provides further information regarding argatroban dosing during CPB, ECMO, VAD use, hemodialysis, and cardiac catheterization. In general, although generally safe anticoagulation with argatroban was reported, further evaluation of the efficacy and safety of argatroban in pediatric patients is needed to make further recommendations.

**Interactions with antiplatelet drugs**

There are no direct interactions between antiplatelet drugs like clopidogrel or aspirin and the DTIs. However, as both, antiplatelet drugs and DTIs affect hemostasis, there is an increased bleeding risk when used concomitantly.

**Switch to oral anticoagulants**

Patients who require long-term anticoagulation beyond the acute period of HIT are most frequently switched to vitamin K antagonists (VKA) like warfarin and phenprocoumon. VKA administration should not be started before the platelet counts have recovered, as a low platelet count is a sign of ongoing active HIT with platelet activation.

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Ideally platelet counts should have reached a stable platform for two consecutive days [85, 86]. We suggest starting with a low dose (expected maintenance dose) of VKA. Concomitant use of both argatroban and VKA is mandatory for a period of ideally seven, but a minimum of five days. Since both agents have an impact on the international normalized ratio (INR), additive effects must be considered before termination of argatroban infusion when using a Quick type prothrombin time (PT) assay. The INR should be ≥ 4.0 on two consecutive days before the argatroban infusion is terminated. This algorithm is applicable for argatroban doses up to 2.0 μg/kg×min. In general as soon as the target INR of ≥4 is achieved at two consecutive days argatroban administration can be stopped. When the INR is assessed by the Owren type PT assay (Scandinavian countries) we suggest aiming for an INR of 3 only. A premature stop of argatroban administration during the transition period to VKA before fully effective VKA effect has been achieved dramatically increases the patient’s risk of thrombosis due to protein C deficiency caused by the VKA.

Conflict of interest statement

The authors received a honorarium for this expert meeting. The corresponding author did receive honoraria from Mitsubishi Pharma for lectures and as a member of the advisory board of the company.

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