Managing argatroban in heparin-induced thrombocytopenia: A retrospective analysis of 729 treatment days in 32 patients with confirmed heparin-induced thrombocytopenia

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Summary
Argatroban is a first-line anticoagulant for patients with heparin-induced thrombocytopenia (HIT). Published data on practical aspects of its use in HIT are lacking. We aim to establish recommendations based on our experience. This cohort of 32 patients is the largest describing cases of HIT confirmed by a functional assay treated with argatroban. Among patients with normal liver function, median starting argatroban doses (SAD) of 0.54, 0.98, and 1.27 μg/kg/min reached steady-state plasmatic argatroban concentrations (PAC) of 0–0.39, 0.40–0.99, and 1.00–1.5 μg/ml, respectively. Median argatroban dose increases (ADI) induced similar median steady-state PAC increases (∆μg/kg/min ≈ ∆μg/ml). PAC measurements performed more than 240 min after SAD or ADI were significantly higher compared to earlier controls. Quantitative PAC measurements and thrombin time (TT) appeared adequate for monitoring. Thirty-eight percent of the thrombotic events were preceded by PAC below 0.4 μg/ml. Four hours after argatroban discontinuation, median international normalised ratio (INR) decrease was −1.2. We suggest: (i) monitoring argatroban with PAC or TT at least 240 min after SAD and/or ADI; (ii) using SAD of 1.0 μg/kg/min and ADI of at least 0.2 μg/kg/min when liver function is normal; (iii) targeting therapeutic PAC of 0.5–1.0 μg/ml; and (iv) targeting INR of 3.5–4.5 when bridging argatroban with vitamin K antagonists.

KEYWORDS
anticoagulation, argatroban, argatroban monitoring, heparin-induced thrombocytopenia, plasmatic argatroban concentration

INTRODUCTION
Heparin-induced thrombocytopenia (HIT) is an adverse effect of unfractionated (UFH) and low-molecular-weight heparin (LMWH), occurring with variable risk depending on the type and dose of heparin and the clinical context.¹⁻³ HIT is characterised by a severe limb- and life-threatening pro-thrombotic state requiring immediate cessation of all heparin and a switch to an alternative non-heparin anticoagulant.⁵⁻⁹ Argatroban is an effective first-line therapy for HIT¹⁰ and was described in a recent meta-analysis as being superior to other parenteral drugs used for the management of HIT.¹¹ Argatroban is a synthetic, reversible and competitive
direct thrombin inhibitor, which binds thrombin on its catalytic site\textsuperscript{12} and is hepatically metabolised.\textsuperscript{13}

Less is known, however, about several practical aspects of anticoagulation with argatroban. The magnitude of starting doses and dose adaptations, as well as the degree of dose reduction required among patients with different types of hepatic dysfunction remain unclear and are performed empirically. Furthermore, despite recent guidelines,\textsuperscript{10} the best timing of, and laboratory assays for, argatroban monitoring still remain open to discussion. The aim of our study was to investigate how argatroban therapy is conducted at our institution and to develop evidence-based in-house recommendations for an optimal anticoagulation with argatroban in patients with HIT.

\textbf{METHODS}

\textbf{Study design}

This was a retrospective observational derivation study. Data were collected between October 2018 and February 2019 and analysed between February 2019 and August 2021.

\textbf{Patient cohort}

Between August 2014 and February 2019, 32 patients with confirmed HIT\textsuperscript{14} [positive anti-PF4/heparin antibodies by HemosIL-Acustar-HIT-IgG (Instrumentation Laboratory GmbH, Munich, Germany) (a chemiluminescent immunoassay, CLIA) and ID-H/PF4-PaGIA (Bio-Rad, DiaMed SA, Basel, Switzerland) (a particle gel immunoassay, PaGIA) and positive heparin-induced platelet aggregation (HIPA, University Hospital, Greifswald, Germany)] received argatroban at our institution and were included in this study.

\textbf{Laboratory monitoring of argatroban}

We performed the following assays on an automated coagulometer (Sysmex CS-5100; Siemens Healthineers, Erlangen, Germany): (i) activated partial thromboplastin time (aPTT; Pathromtin SL\textsuperscript{\textregistered}; Siemens Healthineers, Erlangen, Germany); (ii) thrombin time (TT; Thromboclotin\textsuperscript{\textregistered}, Siemens Healthineers, Erlangen, Germany) with a final thrombin concentration of 1.25 U/ml; and (iii) assessment of the plasma argatroban concentration by a commercial diluted TT assay (Hemoclot Thrombin Inhibitors; Hyphen Biomed, Neuville-sur-Oise, France).

\textbf{Definition of patients with impaired hepatic function}

As argatroban is mainly metabolised in the liver, we divided the studied patients into four categories according to their hepatic dysfunction.

\textbf{FIGURE 1}  
Laboratory parameters. The figure depicts daily platelet counts (G/l, grey), D-dimers (mg/ml, blue) and haemoglobin levels (g/l, red) before and under argatroban therapy in 32 heparin-induced thrombocytopenia (HIT) patients. Points represent median daily values; error bars represent SEM daily values. Note that day 0 is the first day with argatroban treatment [Colour figure can be viewed at wileyonlinelibrary.com]
estimated liver function. 

(i) Normal liver function: serum alanine aminotransferase (ALT) levels less than 180 U/l [three times the upper limit of normal (ULN)] and serum total bilirubin levels less than 25.5 μmol/l.13 When a patient previously had ALT higher than 180 U/l and/or serum total bilirubin higher than 25.5 μmol/l and recovered, he was included into the ‘normal liver function group’ five days after recovery of ALT less than 180 U/l and serum total bilirubin less than 25.5 μmol/l.

(ii) Liver cytolysis: ALT higher than 180 U/l and serum total bilirubin less than 25.5 μmol/l.

(iii) Impaired bilirubin excretion: ALT less than 180 U/l and serum total bilirubin higher than 25.5 μmol/l.

(iv) Liver cytolysis associated with impaired bilirubin excretion: ALT higher than 180 U/l and serum total bilirubin higher than 25.5 μmol/l.

Statistics

Median and interquartile range (IQR) values were calculated with Excel (Microsoft Schweiz GmbH, Zürich-Flughafen, Switzerland). We employed MedCalc (version 15.11.0; MedCalc Software Ltd, Ostend, Belgium) to perform
Passing–Bablock regression analysis. Sigma Plot (version 13.0; Systat Software GmbH, Erkrath, Germany) was used to create Figure 1 and GraphPad Prism (version 8; GraphPad Software, San Diego, USA) was used to create Figures 2–8 and to perform Mann–Whitney tests (t-test, unpaired values, non-parametric distribution), Wilcoxon tests (t-test, paired values, non-parametric distribution) and Spearman correlation measures.

**Figure 3** Effect of magnitude of dose increase and time of monitoring on plasma argatroban concentration in patients with normal liver function. (A) Plasmatic argatroban concentrations (PAC, μg/ml) measured 3–6 h after different magnitudes of argatroban dose increase (ADI, μg/kg/min). We noted significant plasmatic argatroban concentration (PAC) increases with a median of 0.06 μg/ml [interquartile range (IQR) 0–0.17] after argatroban dose increase (ADI) of 0.01–0.10 μg/kg/ml (p-value = 0.0080), 0.15 μg/ml (IQR 0.07–0.26) after ADI of 0.11–0.20 μg/kg/ml (p-value = 0.0016), and 0.21 μg/ml (IQR 0.15–0.28) after ADI of 0.21–0.30 μg/kg/ml (p-value <0.0001). Significant differences in median PAC increases were observed between ADI of 0.01–0.10 versus 0.21–0.30 μg/kg/min (p-value = 0.0007) and ADI of 0.01–0.10 versus 0.31–0.40 μg/kg/min (p-value = 0.047). (B) Plasmatic argatroban concentrations (PAC, μg/ml) measured before or after 3 h after the same magnitude of ADI (+0.11–0.4 μg/kg/min). Median PAC increase in the group with controls performed 3–6 h (median, 240 min) after ADI was 0.19 μg/ml [interquartile range (IQR) 0.14–0.27] and was significantly higher than the median PAC increase in the group with control within 3 h (median, 128 min) after ADI (median, 0.08 μg/ml; IQR 0.04–0.12; p-value = 0.009).
MANAGING ARGATROBAN IN HEPARIN-INDUCED THROMBOCYTOPENIA: A RETROSPECTIVE ANALYSIS OF 729 TREATMENT DAYS IN 32 PATIENTS WITH CONFIRMED HEPARIN-INDUCED THROMBOCYTOPENIA

Ethics

The study complies with the guidelines of the Institutional Ethical Board (Commission Cantonale Vaudoise d’Ethique de la Recherche sur l’Être Humain, CER-VD, protocol number 497/95) and was accepted for quality control assessment of laboratory and clinical management practice.

RESULTS

Patient population

Thirty-two patients with confirmed HIT (15 of them presenting with HIT and thrombosis, HIT-T) were treated with argatroban. Twenty-seven patients (84%) only received argatroban and five (16%) received multiple treatments (Table 1). Overall, we studied 729 argatroban treatment days. Median duration of argatroban therapy was 17.5 days (IQR 10–29.5).

Complications

Compared to the cohort published by Tardy-Poncet et al.,\textsuperscript{15} we registered a higher rate of death related to HIT ($n = 1/32$ vs. 0/16), a similar rate of thromboembolic complications ($n = 13/32$, 41% vs. $n = 7/16$, 44%), and less major bleeding ($n = 4/32$, 13% vs. $n = 3/16$, 19%) and overall death rates ($n = 4/32$, 13% vs. $n = 4/16$, 25%). Individual clinical courses are detailed in Table 2.
We observed 13 thromboembolic events among nine different patients (Table 3). Seven were venous and six were arterial thromboses. Five out of 13 (38%) thromboembolic events were related to an anticoagulation that was probably inadequate. Indeed, PAC had been below 0.4 μg/ml in the 24 h preceding diagnosis in four cases and three days before diagnosis in one patient. Additionally, other risk factors were present: recent surgery and immobilisation (n = 11), systemic infection (n = 8), active cancer (n = 6), body mass index (BMI) higher than 30 kg/m² (n = 2), intravascular devices (n = 5), and/or poor haemodynamic conditions (n = 4).

Concerning the five bleeding events (Table 4), four were considered as major according to the International Society for Thrombosis and Haemostasis (ISTH) definitions.16,17 PAC measured in the 24 h preceding these bleeding events were within target ranges in 4/5 patients. Among the major bleeding events, two intracranial haemorrhages occurred after ischaemic strokes and were considered as secondary to anatomical brain lesions. The other two major bleeding events occurred under concomitant double antiplatelet therapy.

**Outcomes**

Four (13%) patients underwent limb amputation and four patients died (Table 2). Among patients that underwent amputation, three had established advanced peripheral arterial disease. The fourth patient suffered acute hepatic necrosis with ischaemic limb necrosis18 prior to HIT onset and underwent amputation during argatroban therapy (unique patient number, UPN 15.103). Among the four deceased patients, three were still under argatroban therapy at the time of death. In one patient (UPN 16.193), death was directly related to HIT. In two cases, advanced comorbidities may

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**FIGURE 5** Serum total bilirubin levels, steady-state argatroban doses and plasma concentration. Serum total bilirubin levels and steady-state argatroban doses among patients that had a ‘prophylactic’, ‘standard therapeutic’, and ‘high therapeutic’ plasmatic argatroban concentrations (PAC). (A) Serum total bilirubin levels and argatroban dose at steady state among patients that had a ‘prophylactic’ PAC (0–0.39 μg/ml). (B) Serum total bilirubin levels and argatroban dose at steady state among patients that had a ‘standard therapeutic’ PAC (0.4–0.99 μg/ml). (C) Serum total bilirubin levels and argatroban dose at steady state among patients that had a ‘high therapeutic’ PAC (≥1.0 μg/ml).
Evolution of laboratory parameters under argatroban therapy

As depicted in Figure 1, we recorded a median platelet count nadir of 51 G/l on the second day of argatroban therapy, which was followed by full recovery (>150 G/l) on the seventh to eighth day of treatment. In parallel, median D-dimers levels progressively decreased.

Argatroban starting dose

Every starting argatroban dose (SAD, μg/kg/min) and the corresponding PAC measurements (μg/ml) at time $t'$ (min) after SAD were analysed. Among patients with normal liver function, we divided all recorded SAD into two categories,
according to an intended SAD of 0.5 or 1.0 μg/kg/min, respectively.

As illustrated in Figure 2A, after an overall median SAD of 0.5 μg/kg/min (IQR 0.48–0.58), median PAC among controls performed within 240 min reached 0.26 μg/ml (IQR 0.20–0.35) vs. 0.44 μg/ml (IQR 0.29–0.53) in controls at least 240 min after argatroban initiation (p-value = 0.0275). Of note, median SAD administered in patients with monitoring performed after at least 240 min (0.53 μg/kg/min) did not differ significantly from SAD applied in controls less than 240 min (0.50 μg/kg/min; p-value = 0.1594).

Figure 2B shows data for an intended SAD of 1 μg/kg/min (median, 1.04, IQR 0.94–1.09). This led to median PAC of 0.30 μg/ml (IQR 0.14–0.63) among controls less than 240 min versus 0.77 μg/ml (IQR 0.74–0.97) in controls at least 240 min after argatroban initiation, respectively (p-value = 0.0749). Again, median SAD administered in patients with monitoring after at least 240 min (0.98 μg/kg/min) did not significantly differ from SAD applied in controls after less than 240 min (1.06 μg/kg/min, p-value >0.9999).

**Effect of timing of monitoring on plasma argatroban concentration**

Among patients with normal liver function, ADI within a magnitude of 0.11–0.40 μg/kg/min were divided into two groups, based on the timing of monitoring: within 3 h (median, 128 min) or between 3 and 6 h (median, 240 min) after ADI. Figure 3B shows that late monitoring was associated with significantly higher PAC compared to early monitoring, despite the fact that, paradoxically, the median ADI performed in the group with PAC control within 3 h was significantly higher compared to the group with PAC control performed after 3–6 h (median, 0.22 vs. 0.21 μg/kg/min, IQR 0.21–0.26 vs. 0.14–0.22, p-value = 0.048).

**Argatroban dosing adapted to liver function**

Steady-state PAC was defined as no argatroban dose modification in the 6 h preceding monitoring. Patients were...
divided into four categories according to their estimated liver function. For each group, we created PAC intervals according to the treatment aim: (i) ‘prophylactic’ PAC, 0–0.39 μg/ml (Figure 4A); (ii) ‘standard therapeutic’ PAC, 0.40–0.99 μg/ml (Figure 4B); and (iii) ‘high therapeutic’ PAC, 1.00–1.5 μg/ml (Figure 4C). At steady state, patients with normal liver function required median (IQR) argatroban doses of 0.54 μg/kg/min (0.47–1.0), 0.98 μg/kg/min (0.61–1.32), and 1.27 μg/kg/min (0.90–1.45) to reach prophylactic, standard therapeutic, or high therapeutic PAC, respectively. Patients with liver cytolysis required argatroban doses of 0.25 μg/kg/min (0.24–0.29), 0.78 μg/kg/min

**FIGURE 8** Impact of argatroban on the international normalized ratio (INR). (A) INR under vitamin K antagonists (VKA) before and 3 to less than 6 h after argatroban discontinuation. (B) Median INR decrease after argatroban discontinuation. Long bar represents median, short bars represent 95% confidence intervals.
Median argatroban doses were significantly lower in patients with hyperbilirubinaemia compared to patients with normal liver function or liver cytolysis and this was irrespective of the PAC interval. Moreover, among patients with liver cytolysis, median argatroban doses were significantly lower compared to those in patients with normal liver function in the ‘prophylactic’ and ‘high therapeutic’ PAC intervals.

Total bilirubin levels and argatroban doses

Figure 5 depicts argatroban doses at steady state and concomitant bilirubin level, according to the targeted PAC. Among patients that had ‘prophylactic’ (0–0.39 μg/ml; Figure 5A) and ‘standard therapeutic’ (0.40–0.99 μg/ml; Figure 5B) PAC, serum total bilirubin levels and argatroban doses at steady state were strongly inversely correlated [Spearman ρ (95% CI): −0.8203 (−0.9156; −0.6376), p-value: <0.0001, n = 28 pairs and −0.8728 (−0.9185; −0.8041), p-value: <0.0001, n = 77 pairs, respectively]. Inverse correlation was lower among patients that had a ‘high therapeutic’ (≥1.0 μg/ml; Figure 5C) PAC [Spearman ρ (95% CI): −0.5334 (−0.7644; −0.1809), approximate p-value: 0.0042, n = 27 pairs].

Monitoring of argatroban plasma concentration with routine assays

Three different assays for argatroban anticoagulation monitoring were available: aPTT (s), TT (s), and PAC (μg/ml). PAC and corresponding simultaneous TT and aPTT were analysed. PAC and corresponding single TT values showed the highest Spearman correlation [ρ (95% CI): 0.726 (0.689–0.7599); n = 749 pairs], while aPTT and simultaneous PAC showed a lower correlation [ρ (95% CI): 0.590 (0.548–0.630); n = 1031 pairs]. As shown in Figure 6A, increasing TT intervals showed a linear trend, with 80% of TT values higher than 79 s reaching at least a therapeutic PAC (>0.4 μg/ml). Of note, while aPTT intervals within 30–69 s showed a linear trend with the corresponding PAC, aPTT intervals higher than 70 s plateaued (Figure 6B).

(0.53–1.10), and 1.08 μg/kg/min (0.69–1.08) respectively, and patients with hyperbilirubinaemia, argatroban doses of 0.12 μg/kg/min (0.11–0.16), 0.16 μg/kg/min (0.12–0.18), and 0.51 μg/kg/min (0.10–0.51).

### TABLE 1 (Continued)

| Feature                          | Outcomes See also Tables 2–4 |
|----------------------------------|--------------------------------|
| Limb amputation, n (%)           | 4 (13)                         |
| In-hospital mortality, n (%)     | 4 (13)                         |

Abbreviations: CLIA, chemiluminescent immunoassay; HIPA, heparin-induced platelet aggregation; HIT, heparin-induced thrombocytopenia; IQR, interquartile range; IVIG, intravenous immunoglobulin; LMWH, low-molecular-weight heparin; PaGIA, particle gel immunoassay; UFH, unfractionated heparin.

*One patient underwent two operations (cardiac and vascular surgery) on the same day.

*One patient received plasmapheresis and then IVIG after argatroban discontinuation.

Median argatroban doses were significantly lower in patients with hyperbilirubinaemia compared to patients with normal liver function or liver cytolysis and this was irrespective of the PAC interval. Moreover, among patients with liver cytolysis, median argatroban doses were significantly lower compared to those in patients with normal liver function in the ‘prophylactic’ and ‘high therapeutic’ PAC intervals.
### Table 2: Patients’ individual clinical course

| Sex   | Age | Disease and management at our institution                                                                 | Type of heparin and dose | Platelet count nadir value (G/l) | 4T score | HIT versus HIT-T | HIT-T: Type of thrombo-embolic event at diagnosis | Diagnostic work-up                                                                 |
|-------|-----|-----------------------------------------------------------------------------------------------------------|--------------------------|----------------------------------|----------|------------------|-----------------------------------------------|-----------------------------------------------------------------------------------|
| 1.    | F   | Thoracic surgery; idiopathic pulmonary fibrosis and bilateral lung transplant                              | Prophylactic UFH, then prophylactic LMWH | 51                               | 5        | HIT-T            | Pulmonary embolism and internal jugular vein thrombosis (secondary to catheter & HIT) | Chest CT scan with contrast product ultrasonography by an angiologist               |
| 2.    | F   | Cardiac surgery; pheochromocytoma and right adrenaectomy vena cava and right atrium thrombi thrombectomies | Therapeutic UFH, then therapeutic LMWH | 111                              | 5        | HIT              | None                                          | N/A                                                                               |
| 3.    | M   | Cardiac and vascular surgery; ischaemic heart disease with triple coronary bypass; left carotid stenosis with carotid endarterectomy (two simultaneous operations) | Prophylactic UFH, then prophylactic LMWH | 48                               | 4        | HIT              | None                                          | N/A                                                                               |
| 4.    | M   | Cardiac surgery; severe aortic valve stenosis with bioprosthetic aortic replacement valve                | Prophylactic UFH, then prophylactic LMWH | 18                               | 5        | HIT              | None                                          | N/A                                                                               |
| 5.    | M   | Cardiac surgery; ischaemic heart disease with triple coronary bypass; severe aortic valve stenosis and bioprosthetic aortic replacement valve | Prophylactic UFH, then prophylactic LMWH | 54                               | 5        | HIT-T            | Fibular artery thrombosis                     | Ultrasonography and plethysmography by an angiologist                             |
| 6.    | F   | Internal medicine; systemic lupus erythematosus with antiphospholipid antibodies syndrome and heparin anticoagulation | Prophylactic UFH, then therapeutic UFH | 5                                 | 5        | HIT              | None                                          | N/A                                                                               |
| 7.    | F   | Cardiology; acute heart failure and anticoagulation for mechanical mitral valve                         | Therapeutic UFH, then prophylactic UFH | 79                               | 4        | HIT              | None                                          | N/A                                                                               |
| 8.    | M   | Intensive care unit; septic shock secondary to Balthazar E pancreatitis                                  | Prophylactic UFH          | 16                               | 4        | HIT              | None                                          | N/A                                                                               |
| 9.    | M   | Vascular surgery; bilateral advanced arterial peripheral artery disease with two arterio-arterial bypasses, one Fogarty thrombo-embolectomy and one thrombolysis | Therapeutic UFH           | 49                               | 6        | HIT-T            | External iliac artery and commune femoral artery thrombosis | Ultrasonography and plethysmography by an angiologist; arterial CT scan with contrast product |
| 10.   | M   | Cardiology; ischaemic heart disease with cardiogenic shock and angioplasty with stenting                | Therapeutic UFH and then prophylactic UFH | 30                               | 4        | HIT-T            | Internal jugular vein thrombosis (secondary to catheter & HIT) | Ultrasonography by an angiologist                                                  |
| CLIA (U/ml) | PaGIA (titre) | Type of treatment and duration (days) | Thrombo-embolic events during treatment YES/NO | Bleeding events YES/NO | Limb outcome: Amputation and day of Argatroban treatment | Final outcome: Discharge xxx days after diagnosis of HIT versus hospital transfer |
|------------|--------------|--------------------------------------|-----------------------------------------------|------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------|
| 7.03       | 8            | Argatroban; 11 days Central venous catheter (jugular) already removed at time of HIT diagnosis | No                                           | No                     | No amputation                                           | Hospital transfer 11 days after diagnosis of HIT |
| 11.70      | 16           | Argatroban; 10 days YES: 1* (SVT LLL) | NO                                           | NO                     | No amputation                                           | Discharged 14 days after diagnosis of HIT |
| 28.00      | >16          | Argatroban; 18 days NO                | NO                                           | NO                     | No amputation                                           | Discharged 24 days after diagnosis of HIT |
| 12.56      | >16          | Argatroban; 18 days IVIG NO           | YES; 1* (minor bleeding; spontaneous haematoma on the arms and forearms)* | No amputation          | Hospital transfer 18 days after diagnosis of HIT        |
| 70.88      | 16           | Argatroban; 14 days NO                | NO                                           | NO                     | No amputation                                           | Discharged 23 days after diagnosis of HIT |
| 1.40       | 16           | Danaparoid; 2 days then argatroban; 19 days IVIG NO | NO                                           | NO                     | No amputation                                           | Discharged 22 days after diagnosis of HIT |
| 10.24      | 8            | Argatroban; 24 days NO                | NO                                           | NO                     | No amputation                                           | Discharged 32 days after HIT diagnosis |
| 12.42      | >32          | Danaparoid; 8 days argatroban; 47 days NO | NO                                           | NO                     | No amputation                                           | Discharged 104 days after HIT diagnosis |
| >128       | 8            | Argatroban; 44 days; prosthetic bypass confection; lower left limb YES: 4* (1x arterial prosthetic bypass; 1x PE 1x DVT 1x arterial; lower left proximal limb) | NO                                           | Gritt amputation of right lower limb 16 days after HIT diagnosis | Deceased 44 days after HIT diagnosis (pneumonia with cardiac failure) |
| 2.14       | 004          | Argatroban; 28 days, IVIG plasmapheresis because of discontinuation of argatroban (haemorrhagic shock) NO | YES; 1* (major bleeding; haemorrhagic shock after self-snatch of urinary catheter in the context of confusional state) | NO                     | No amputation                                           | Discharged 69 days after HIT diagnosis |
| Sex  | Age | Underlying disease(s) and management at our institution | Type of heparin and dose | Platelet count nadir value (G/l) | 4T score | HIT versus HIT-T | HIT-T: Type of thrombo-embolic event at diagnosis | Diagnostic work-up |
|------|-----|-------------------------------------------------------|--------------------------|---------------------------------|---------|----------------|-----------------------------------------------|-------------------|
| F    | 73  | Cardiac surgery; ischaemic heart disease, ascendant aorta aneurysm with moderate aortic valve regurgitation. Triple coronary bypass, bioprothetic aortic replacement valve and ascendant aorta replacement | Therapeutic and then prophylactic UFH | 62 | 5 | HIT | None | N/A |
| F    | 53  | Intensive care unit; second-degree burns on 14% of body surface area, including sub-glottic burn | Prophylactic LMWH | 134 | 5 | HIT-T | Pulmonary embolism | Chest CT scan with contrast product |
| M    | 64  | Thoracic surgery; mediastinal sarcoma with vena cava superior infiltration and tumour resection | Prophylactic UFH, then therapeutic UFH and then prophylactic LMWH | 75 | 5 | HIT-T | Bilateral pulmonary embolism | Chest CT scan with contrast product |
| M    | 59  | Thoracic surgery; empyema and thoracoscopy with pulmonary decortication | Prophylactic LMWH | 134 | 5 | HIT-T | Pulmonary embolism | Chest CT scan with contrast product |
| M    | 81  | Cardiac surgery; severe aortic valve stenosis and bioprothetic aortic replacement valve | Therapeutic LMWH and then prophylactic UFH | 71 | 5 | HIT | None | N/A |
| M    | 71  | Vascular surgery; abdominal aorta aneurysm and vascular endoprosthesis | Prophylactic UFH | 32 | 5 | HIT | None | N/A |
| M    | 48  | Intensive care unit; second-degree burns on 14% of body surface area, including sub-glottic burn | Prophylactic LMWH and then therapeutic UFH (HIT-T) | 79 | 6 | HIT-T | Deep vein and superficial vein thrombosis | Ultrasonography by an angiologist |
| F    | 67  | Cardiac surgery; ascendant and descendant thoracic, suprarenal abdominal aortic ecstasia with prosthctic replacement of ascending aorta and thoracic aorta endoprosthesis | Prophylactic UFH | 25 | 5 | HIT | None | N/A |
| M    | 50  | Cardiology; anterior STEMI with angioplasty and stenting | Prophylactic, then therapeutic, then prophylactic UFH | 56 | 7 | HIT-T | Bilateral pulmonary embolism and bilateral deep vein thrombosis | Chest CT scan with contrast product ultrasonography by an angiologist |
| F    | 53  | Intensive care unit; perimyocarditis with cardiogenic shock, septic shock and disseminated intravascular coagulation with heparin anticoagulation | Prophylactic, then therapeutic UFH | 19 | 5 | HIT | None | N/A |
| CLIA (U/ml) | PaGIA (titre) | Type of treatment and duration (days) | Thrombo-embolic events during treatment YES/NO (see Table 3) | Bleeding events YES/NO (see Table 4) | Limb outcome: Amputation and day of Argatroban treatment | Final outcome: Discharge xxx days after diagnosis of HIT versus hospital transfer |
|-------------|---------------|--------------------------------------|-------------------------------------------------------------|--------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------------------------|
| 2.98        | N.A.          | Argatroban; 10 days                  | NO                                                          | NO                                   | No amputation                                              | Discharged 13 days after HIT diagnosis                                           |
| 2.05        | >32           | Argatroban; 3 days                   | YES: 1* (internal carotid artery thrombosis and stroke)     | YES: 1* (intracranial bleeding secondary to ischaemic stroke) | No amputation                                              | Deceased 3 days after diagnosis of HIT (massive PE, pneumonia, intracranial bleeding with cerebral herniation) |
| 20.71       | >32           | Argatroban; 8 days                   | NO                                                          | NO                                   | No amputation                                              | Discharged 8 days after HIT diagnosis                                             |
| 1.70        | 8             | Argatroban; 10 days                  | NO                                                          | NO                                   | No amputation                                              | Discharged 15 days after HIT diagnosis                                             |
| >128        | >32           | Argatroban; 29 days                  | NO                                                          | NO                                   | No amputation                                              | Discharged 31 days after HIT diagnosis                                             |
| 1.09        | >16           | Argatroban; 13 days                  | NO                                                          | NO                                   | No amputation                                              | Discharged 14 days after HIT diagnosis                                             |
| 1.00        | 2             | Argatroban; 49 days                  | NO                                                          | NO                                   | No amputation                                              | Discharged 93 days after HIT diagnosis                                             |
| 33.15       | >16           | Argatroban; 31 days                  | NO                                                          | NO                                   | No amputation                                              | Discharged 79 days after HIT diagnosis                                             |
| 0.74        | 8             | Danaparoid; 6 days and then argatroban; 109 days | NO                                                          | NO                                   | 1: Left lower limb Gritti amputation 13 days after HIT diagnosis 2: Right heel necrosectomy 43 days after HIT diagnosis 3: Left fingers 2, 3, 4, 5 amputations 50 days after HIT diagnosis 4: Right fingers 2, 3, 4 amputation and right foot toes 1, 3, 4, 5 amputation 104 days after HIT diagnosis NB: patient suffered acute hepatic necrosis and ischaemic limb necrosis before onset of HIT | Discharged 155 days after HIT diagnosis                                           |

(Continues)
| Sex | Age | Care unit; underlying main disease(s) and management at our institution | Type of heparin and dose | Platelet count nadir value (G/l) | HIT versus HIT-T | HIT-T: Type of thromboembolic event at diagnosis | Diagnostic work-up |
|-----|-----|-------------------------------------------------|--------------------------|-------------------------------|-------------------|---------------------------------------------|-------------------|
| 20. UPN: 14.038 | M | 61 | Thoracic surgery; metastatic neuro-endocrine tumour and exploratory thoracotomy with oncologic surgery | Prophylactic, then therapeutic UFH | 25 | 4 | HIT | None | thrombin time N/A |
| 21. UPN: 14.049 | F | 78 | Internal medicine; metastatic small-cell lung carcinoma and chemotherapy | Port-a-cath flushing with UFH, then therapeutic LMWH, then therapeutic UFH | 23 | 4 | HIT-T | Pulmonary embolism and internal jugular and subclavian veins thrombosis | Chest CT scan with contrast product ultrasoundography by an angiologist |
| 22. UPN: 14.072 | F | 83 | Neurosurgery; glioblastoma and radiochemotherapy | Prophylactic UFH | 63 | 5 | HIT-T | Multiple pulmonary embolisms | Chest CT scan with contrast product ultrasoundography by an angiologist |
| 23. UPN: 15.001 | M | 72 | Intensive care unit; metastatic prostate adenocarcinoma with pleural carcinosis and right thoracotomy with right pleural decortication | Prophylactic, then therapeutic UFH | 56 | 5 | HIT-T | Radial artery thrombosis (when radial catheter was removed) | Ultrasoundography by an angiologist |
| 24. UPN: 15.138 | M | 60 | Vascular surgery; peripheral artery embolies with rapidly progressive lower limb ischaemia and lower limb bypass and thrombolysis | Therapeutic UFH | 63 | 7 | HIT-T | Aorto-iliac and infra-renal aorta aneurysm thrombosis | Ultrasoundography by an angiologist; vascular CT scan with contrast product |
| 25. UPN: 15.143 | F | 86 | Cardiac surgery; ascendant aorta aneurysm and ascending aorta replacement | Prophylactic UFH, then prophylactic LMWH, then prophylactic UFH | 35 | 5 | HIT | None | N/A |
| 26. UPN: 15.160 | F | 66 | Vascular surgery; advanced bilateral peripheral artery disease and angioplasty with stenting, thrombolysis, Fogarty thrombectomy, bypass and endarterectomy | Prophylactic, then therapeutic UFH | 82 | 6 | HIT-T | Bilateral superficial femoral artery and venous popliteo-poplital bypass thrombosis | Ultrasoundography by an angiologist |
| 27. UPN: 15.166 | F | 54 | Cardiac surgery; severe aortic valve stenosis associated with ascendant aorta dilatation. Mechanic aortic replacement valve and ascending aorta replacement | Prophylactic, then therapeutic UFH | 14 | 6 | HIT | None | N/A |
| 28. UPN: 15.169 | M | 57 | Cardiac surgery; coronary heart disease and coronary bypass | Prophylactic LMWH | 23 | 6 | HIT-T | Splanchnic vein thrombosis with mesenteric ischaemia | Chest and abdominal CT with contrast product |
| CLIA (U/ml) | PaGIA (titre) | Type of treatment and duration (days) | Thrombo-embolic events during treatment YES/NO *see Table 3 | Bleeding events YES/NO *see Table 4 | Limb outcome: Amputation and day of Argatroban treatment | Final outcome: Discharge xxx days after diagnosis of HIT versus hospital transfer |
|-------------|---------------|-------------------------------------|----------------------------------------------------------|--------------------------------------|----------------------------------------------------------|------------------------------------------------------------------|
| 0.15        | 4             | Argatroban; 17 days                 | YES: 1* (bilateral PE)                                   | NO                                   | No amputation                                            | Discharged 28 days after HIT diagnosis                             |
| 11.84       | 32            | Argatroban; 8 days                  | Check; YES!                                              | NO                                   | No amputation                                            | Discharged 8 days after HIT diagnosis                              |
| 14.16       | 32            | Cava filter on day –5 of treatment argatroban; 24 days | YES: 1* (vena cava filter and bilateral pelvic veins thrombosis) | NO                                   | No amputation                                            | Deceased 46 days after HIT diagnosis                               |
| 24.62       | 32            | Argatroban; 5 days                  | NO                                                      | NO                                   | No amputation                                            | Deceased 5 days after HIT diagnosis (metastatic prostatacarcinoma with pleural carcinosis and global respirator insufficiency) |
| 2.77        | 32            | Argatroban; 19 days                 | NO                                                      | NO                                   | Gritti amputation of right lower limb 4 days after HIT diagnosis | Discharged 59 days after HIT diagnosis                             |
| 28.7        | 32            | Argatroban; 8 days                  | NO                                                      | NO                                   | No amputation                                            | Discharged 12 days after HIT diagnosis                             |
| 1.37        | 8             | Argatroban; 21 days Left lower limb prothetic bypass between superficial femoral artery and popliteal artery | NO                                                      | YES* 1 major bleeding; hematochezia (argatroban; ASS cardio and clopidogrel) 1 minor bleeding; melena (argatroban and clopidogrel) | Burgess amputation of left lower limb 8 days after HIT diagnosis | Discharged 72 days after HIT diagnosis                             |
| 17.97       | 8             | Argatroban; 16 days                 | NO                                                      | NO                                   | No amputation                                            | Discharged 17 days after HIT diagnosis                             |
| 26.16       | 8             | Argatroban; 21 days median laparotomy; resection of 1.5 m of bowel | YES* thrombosis of principal left thumb artery          | NO                                   | No amputation resection of 1.5 m of ischaemic bowel 1 day after HIT diagnosis | Discharged 23 days after HIT diagnosis                             |

(Continues)
Impact of argatroban on values of the international normalised ratio

Figure 8 depicts median international normalized ratio (INR) among patients ($n = 11$) treated with VKA and argatroban. Median INR was 4.5 immediately before argatroban discontinuation and 2.9 measured 3–6 h (median, 263 min) following argatroban discontinuation (median INR decrease –1.2, IQR INR decrease –0.7 to –1.7).

DISCUSSION

In order to develop evidence-based in-house recommendations for argatroban dosing and monitoring we analysed a cohort of 32 patients with confirmed HIT, about half of them ($n = 15, 47\%$) presenting with HIT-T (Table 1). Median anticoagulation duration was 17.5 days (IQR 10–29.5, range 3–109) for a total of 729 treatment days. As depicted in Figure 1, argatroban was biologically effective, enabling progressive decrease of D-dimers and platelet count normalisation within 7–8 days of treatment, without causing a drop of haemoglobin levels. These results are in line with those presented in our previous publication.6
The effect of timing of first monitoring on the plasma argatroban concentration

Our results do not support the recommendation of performing the first laboratory control 2h after starting argatroban. Among patients with normal liver function, a steady-state plasmatic concentration is reached at the earliest 4h after starting argatroban, both in case of a SAD of 0.5µg/kg/min (Figure 2A) and 1.0µg/kg/min (Figure 2B). Based on our observations, we estimate a plasmatic argatroban half-life of approximately 1h (Figure 7A), which agrees with published data. Our results are in line with those of Tardy-Poncet et al., who noted that argatroban concentrations measured 2h after SAD were lower than steady-state concentrations determined later (i.e., 0.39±0.29µg/ml vs. 0.61±0.28µg/ml respectively). Based on these results and since four to five drug half-lives are necessary to reach plasma steady state after starting administration, we suggest performing the first PAC control at least 4h after SAD.

The effect of the dose adjustments and timing of monitoring on subsequent plasma argatroban concentrations

To our knowledge, there is only one publication that assessed the magnitude of argatroban dose adaptations and their impact on consecutive PAC. Recent guidelines on management of patients with HIT did not give recommendations on this issue. Our data show that: (i) ADI intervals of 0.01–0.10, 0.11–0.20, 0.21–0.30, and 0.31–0.4µg/kg/min lead to significant PAC increases (Figure 3A); (ii) a given ADI induced a roughly similar median PAC increase (i.e., ΔADI µg/kg/min = Δ PAC µg/ml); and (iii) significant differences in PAC increases were observed between ADI of 0.01–0.10
### Table 3: Thromboembolic events under argatroban anticoagulation

| HIT type | Timing of the thromboembolic event; day of argatroban treatment | Type and localisation | Argatroban dosage in the 24 h preceding the TE diagnosis; mean (detailed doses), μg/kg/min | PAC measured in the 24 h preceding the TE diagnosis; mean (μg/ml) | Minimal PAC measured in the 24 h preceding the TE diagnosis (μg/ml) | Additional thrombotic risk factors |
|----------|---------------------------------------------------------------|-----------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------|-----------------------------------|
| 1. UPN: 18.022 | HIT 4th | Deep vein thrombosis | 1.39 (1.33; 1.45) | 0.59 | 0.35<sup>b</sup> | High BMI; recent surgery; immobilisation; active cancer; systemic infection (urosepsis) |
| 2. UPN: 18.148 | HIT-T 2nd | Femoro-iliac arterial prosthetic bypass thrombosis | 0.65 (1.0; 0.5; 0.45) | 1.04 | 0.91 | Recent surgery; immobilisation; systemic infection (pneumonia) |
| 3. UPN: 18.148 | HIT-T 28th | Bilateral lung emboli | 0.5 (0.5) | 0.45 | 0.43; NB: 0.26; there might be a diagnostic delay of the lung emboli<sup>bc</sup> | Recent surgery; immobilisation; systemic infection (pneumonia) |
| 4. UPN: 18.148 | HIT-T 36th | Superficial femoral and popliteal arteries thrombosis | 0.6 (0.5; 0.59; 0.7) | 0.56 | 0.36<sup>b</sup> | Low blood flow; possibly insufficient anticoagulation<sup>a</sup> |
| 5. UPN: 16.193 | HIT-T 2nd | Internal carotid artery thrombosis and subsequent ischaemic stroke | 0.55 (0.5; 0.59) | 0.53 | 0.21<sup>b</sup> | High BMI; recent surgery; immobilisation; active cancer; systemic infection (pneumonia) |
| 6. UPN: 14.038 | HIT 4th | Bilateral lung emboli | 0.37 (0.12; 0.39; 0.6) | 0.5 | 0.22<sup>b</sup> | Recent surgery; immobilisation; active cancer |
| 7. UPN: 14.049 | HIT-T 4th | Subclavian vein and internal jugular vein thrombosis | 0.53 (0.45; 0.48; 0.5; 0.52; 0.69) | 0.20 | 0.11 | Active cancer; subclavian catheter for chemotherapy |
| 8. UPN: 14.072 | HIT-T 8th | Vena cava filter thrombosis | 1.32 (1.21; 1.42) | 0.38 | 0.3 | Recent surgery; immobilisation; active cancer |
| 9. UPN: 14.072 | HIT-T 14th | Vena cava filter thrombosis extension and bilateral pelvic veins thrombosis | 1.86 (1.86) | 0.66 | 0.63 | Recent surgery; immobilisation; active cancer |
### Table 3 (Continued)

| HIT type | Day of argatroban treatment | Type and localization | Argatroban dosage in the 24 h preceding the TE diagnosis; mean (detailed doses), μg/kg/min | PAC measured in the 24 h preceding the TE diagnosis; mean (μg/ml) | Minimal PAC measured in the 24 h preceding the TE diagnosis (μg/ml) | Additional thrombotic risk factors |
|----------|-----------------------------|-----------------------|-----------------------------------------------|--------------------------|-----------------------------------------------|----------------------------------|
| 10. UPN: 15.169 | HIT-T | 2nd | Main thumb artery thrombosis | 0.61 (0.92; 0.92) | 0.28 | 0 | Recent surgery; systemic infection secondary to mesenteric ischaemia; radial artery catheter |
| 11. UPN: 15.186 | HIT | 15th | Intra-cardiac thrombus with subsequent cardio-embolic occipital strokes | 2.29 (2.29) | 0.58 | 0.49 | Immobilisation; advanced heart failure (dilatative cardiomyopathy with intra-ventricular thrombus); coronary and ventricular multiple catheterisms |
| 12. UPN: 18.243 | HIT | 3rd | Left coronary leaflet of the aortic valve thrombosis | 0.27 (0.23; 0.29; 0.25; 0.29) | 0.50 | 0.37 | Recent surgery; immobilisation; systemic infection (pneumonia with sepsis); heart failure with reduced EF (because of an aortic valve briefly and partially opening 1/10 cardiac cycles) and ventricular dilatation; left jugular central venous catheter |
| 13. UPN: 18.243 | HIT | 27th | Internal jugular vein and subclavian vein thrombosis | 0.35 (0.35) | 0.75 | 0.65 | Recent surgery; immobilisation; systemic infection (pneumonia with sepsis); heart failure with reduced EF and ventricular dilatation; left jugular central venous catheter |

Five thromboembolic events were related to a possibly insufficient anticoagulation (*a*). Among them, four events were preceded by a minimum PAC below 0.4 μg/ml (*b*) in the 24 h preceding the diagnosis. One event might have been diagnosed with delay, being preceded by a minimum PAC below 0.4 μg/ml three days before diagnosis confirmation (*c*). Three thromboembolic events were partially or fully related to poor haemodynamic s; two events were associated with advanced cardiac failure with severely reduced ejection fraction (*d*) and one was associated with low blood flow through a prosthetic vascular bypass in a patient with advanced peripheral arterial disease (*e*). Five thromboembolic events were related to intravascular foreign material (*f*).

Abbreviations: BMI, body mass index; EF, ejection fraction; HIT, heparin-induced thrombocytopenia; HIT-T, HIT and thrombosis; PAC, plasmatic argatroban concentrations; TE, thrombotic event; UPN, unique patient number. Bold indicate mean values.
**TABLE 4**  Bleeding events under argatroban anticoagulation

| HIT type | Day of argatroban treatment | Timing of bleeding event; | Blood products administered | Argatroban dosage in the 24 h preceding the TE diagnosis; | Mean PAC (μg/ml) measured in the preceding 24 h (day prior diagnosis and day of diagnosis of the bleeding event) | Maximal PAC (μg/ml) measured in the preceding 24 h (day prior diagnosis and day of diagnosis of the bleeding event) | Additional bleeding risk factors (bleeding history—reduced haemoglobin—concomitant antiplatelet drug—renal impairment — anatomical lesions — recent surgery) | Suspected cause of bleeding events (excessive anticoagulation and antiaggregation versus anatomical lesion vs. undetermined) |
|----------|-----------------------------|--------------------------|----------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| 1. UPN: 17.222 | HIT 2nd | Minor bleeding; subcutaneous spontaneous haematoms on both upper limbs | 0 | 0.43 (0.25; 0.45; 0.58) | 0.23 | 0.33 | Recent aortic valve replacement; impaired renal function | Undetermined |
| 2. UPN: 17.042 | HIT-T 2nd | Major bleeding; macrohema turia and jugular bleeding with haemorrhagic shock \(^b\) | 3 units of packed red blood cells; 1 unit of fresh frozen plasma | 0.92 (0.92) | 0.55 | 0.77 | Vesical, prostatic and ureteral lesions secondary to self-removal of urinary catheter; internal jugular vein lesion secondary to self-snatch of central venous catheter clopidogrel and aspirin treatments (recent stenting of RIVA); renal impairment; reduced haemoglobin | Anatomical lesion; possibly ‘excessive’ antiaggregation |
| 3. UPN: 16.193 | HIT-T 3rd | Intracerebral bleeding with cerebral herniation \(^a\) | 0 | 0.59 (0.59) | 0.59 | 0.69 | Recent ischaemic stroke secondary to thrombosis of the right internal carotid artery | Anatomical lesion |
| 4. UPN: 15.160 | HIT-T 9th | Major bleeding; hematochezia secondary to peri-operative ischaemic colitis \(^b\) | 2 units of packed red blood cells | Mean: 0.39 (0; 0.41; 0.61; 0.52) | 0.26 | 0.45 | Clopidogrel and aspirin treatments; reduced haemoglobin due to digestive angiodysplasia Ischaemic colitis | Anatomical lesion and possibly ‘excessive’ anti-aggregation |
| 5. UPN: 15.186 | HIT 20th | Major bleeding; asymptomatic bilateral frontal intracerebral bleedings and left intracerebellar bleeding \(^a\) | 0 | 2.29 (2.29) | 0.58 | 0.67 | Multiple cardio-embolic cerebral and cerebellar strokes | Anatomical lesion |

**Note:** We observed five bleeding events, four of them being major and one of them being minor, according to the ISTH definition.\(^{16,17}\) Mean and maximal PAC (μg/ml) measured in the 24 h preceding these five bleeding events seemed not to be excessive. Bold indicate mean values.

**Abbreviations:** HIT, heparin-induced thrombocytopenia; PAC, plasmatic argatroban concentrations; RIVA, ramus interventricularis anterior; TE, thrombotic event; UPN, unique patient number.

\(^a\)Among the four major bleeding events, two were intracranial bleedings that occurred after ischaemic stroke.

\(^b\)The two other major bleeding events occurred under concomitant double antiplatelet therapy (aspirin and clopidogrel) and were related to anatomical lesions.
Correct timing of laboratory monitoring is crucial for obtaining a reliable result. However, to the best of our knowledge, there are no published data concerning this practical issue. Similarly to what we have observed with initial monitoring (Figure 2), we show in Figure 3B that after ADI of 0.1–0.4 μg/kg/min, median PAC increase was significantly greater when laboratory control was performed 'late' (after 3 to up to 6 h) compared to 'early' controls (within 3 h). Hence, this underscores that timing of control after argatroban dose adaptation is critical and we suggest waiting 4 h after dose adaptation among patients with normal liver function.

### The effect of liver function on argatroban dosing

The argatroban dose required to reach a given target PAC depends on liver function. As suggested by Levine et al., serum total bilirubin might be more useful than ALT to identify patients who require dose reduction. Based on the alteration of bilirubin and/or ALT, we defined four different hepatic impairment patterns (Figure 4). Patients with increased bilirubin levels required significantly lower argatroban steady-state doses than patients with normal liver function irrespective of the target PAC interval. Patients with liver cytolysis tended to require lower median argatroban doses at steady state than patients with normal liver function.

### TABLE 5 Standardised in-house management of HIT patients with argatroban

| Monitoring of platelets and D-dimers | Normal liver function | Impaired liver function | Isolated liver cytolysis | Multiorgan dysfunction* |
|-------------------------------------|-----------------------|-------------------------|--------------------------|-------------------------|
| Monitoring of hepatic function      |                       |                         |                          |                         |
| Before SAD, then at discretion of physician | Once daily | Before SAD, then at discretion of physician | Before SAD, then at discretion of physician | Before SAD, then at discretion of physician |
| SAD (μg/kg/min)                     | 1.0                   | 0.25                    | 0.75                     | 0.50                    |
| Timing of monitoring after SAD (hours) | 4 h; repeat twice at 4 h each if no ADA, afterwards once daily in ss | 6 h; repeat twice at 6 h each if no ADA, afterwards once daily in ss | 4 h; repeat twice at 4 h each if no ADA, afterwards once daily in ss | 4 h; repeat twice at 4 h each if no ADA, afterwards once daily in ss |
| ss-PAC target (μg/ml)               | 0.5–1.0               | 0.5–1.0                 | 0.5–1.0                  | 0.5–1.0                 |
| ss-TT target (s)                    | 80–120                | 80–120                  | 80–120                   | 80–120                  |
| ss-aPTT target (fold increase and s) | 1.7–2.4 × baseline value (max. 70–75 s) | 1.7–2.4 × baseline value (max. 70–75 s) | 1.7–2.4 × baseline value (max. 70–75 s) | 1.7–2.4 × baseline value (max. 70–75 s) |
| Magnitude of ADA (μg/kg/min)        | Adapted to first PAC/TT and to ss-PAC-targeted; Δ ADA μg/kg/min = Δ PAC μg/ml (at least 0.2 μg/kg/min) | Adapted to first PAC/TT and to ss-PAC-targeted; Δ ADA μg/kg/min = 2Δ PAC μg/ml (0.05–0.1 μg/kg/min) | Adapted to first PAC/TT and to ss-PAC-targeted; Δ ADA μg/kg/min = Δ PAC μg/ml (0.2 μg/kg/min) | Adapted to first PAC/TT and to ss-PAC-targeted; Δ ADA μg/kg/min = Δ PAC μg/ml (0.2 μg/kg/min) |
| Timing of monitoring after ADA      | 4 h; repeat 4 h after each ADA | 6 h; repeat 6 h after each ADA | 4 h; repeat 4 h after each ADA | 4 h; repeat 4 h after each ADA |
| Frequency of PAC/TT/aPTT monitoring | Once daily after 3 target ss-PAC/TT | Once daily after 3 target ss-PAC/TT | Once daily after 3 target ss-PAC/TT | Once daily after 3 target ss-PAC/TT |
| When bridging to AVK: target INR on argatroban | 3.5–4.5 | 3.5–4.5 | 3.5–4.5 | – |
| When bridging to AVK: timing of INR after argatroban stop | After 4 h | After more than 4 h | After 4 h | – |

Abbreviations: ADA, argatroban dose adaptation; aPTT, activated partial thromboplastin time; AVK, vitamin K antagonist; INR, international normalised ratio; SAD, starting argatroban dose; ss, steady state; TT, thrombin time (see Methods).

*Multi-organ dysfunction without impaired bilirubin excretion.

Use SAD of 0.25 μg/kg/min among patients with mild to moderate bilirubin excretion impairment and consider danaparoid for patients with severe bilirubin excretion impairment.

See results in paragraph "Argatroban dosing adapted to liver function".

Target higher PAC (1–1.5 μg/ml) in case of insufficient platelet count recovery and/or D-dimers level decrease.

Reagent- and coagulometer-specific values, not generalisable.

μg/kg/min and 0.21–0.30 μg/kg/min and between ADI of 0.01–0.10 μg/kg/min and 0.31–0.40 μg/kg/min.

The argatroban dose required to reach a given target PAC depends on liver function. As suggested by Levine et al., serum total bilirubin might be more useful than ALT to identify patients who require dose reduction. Based on the alteration of bilirubin and/or ALT, we defined four different hepatic impairment patterns (Figure 4). Patients with increased bilirubin levels required significantly lower argatroban steady-state doses than patients with normal liver function irrespective of the target PAC interval. Patients with liver cytolysis tended to require lower median argatroban doses at steady state than patients with normal liver function.
function, in order to reach prophylactic and high therapeu-
tic PAC intervals. Our data confirm that impaired bilirubin
excretion plays the most important role in decision-making
for argatroban dosing and indicate that patients with liver
cytolysis probably require smaller argatroban dose re-
ductions compared to patients with impaired bilirubin
excretion.

The extent of bilirubinaemia and
argatroban dosing

A total plasma bilirubin level higher than 25.5 μmol/l has
been proposed to identify patients with impaired biliru-
bin excretion, thus requiring argatroban dose reduction. 13
However, as presented in Figure 5, we could not iden-
tify a critical serum total bilirubin threshold, observing
a progressive impact on the required dosage in order to
achieve a prophylactic (Figure 5A), standard therapeutic
(Figure 5B), or high therapeutic PAC (Figure 5C) already
at bilirubin values within reference range. Based on our
data, we suggest to consider reducing argatroban doses
among patients with serum total bilirubin levels above
20 μmol/l, which is lower than the threshold suggested by
Levine et al. 13

Argatroban laboratory monitoring with
aPTT and thrombin time

Activated partial thromboplastin time is the most widely
available laboratory assay for monitoring argatroban
anticoagulation and is currently recommended by the
American Society of Hematology (ASH) guidelines. 10
However, multiple factors might affect its results, leading
to inaccurate monitoring, which in turn may result in ar-
gatroban under-dosing and thrombosis progression. 21 Our
group and others have shown that TT is more reliable and
robust for the monitoring of argatroban. 6,22 Figure 6A con-
fers a linear relationship between PAC and correspond-
ing TT intervals. In contrast, the relationship between
increasing PAC and correspondent simultaneous aPTT
intervals is not linear, reaching a plateau for aPTT values
above 70 s (Figure 6B), underscoring that this coagulation
assay is less accurate for monitoring argatroban anticoag-
ulation. 6,21,22 We therefore suggest to monitor argatroban
by TT when the assessment of PAC with a commercially
diluted TT assay is not available. From an analytical point
of view, it would be better to employ two TTs, e.g. with
final thrombin concentrations of 1.5 and 5 U/ml as we did
in our previous work. 6,24 However, our current experi-
ence indicates that also a single TT with a final thrombin
concentration of 1.25 U/ml is adequate up to argatroban
concentrations of about 1 μg/ml (Figure 6A). Monitoring
argatroban with thrombin-time-based assays is in line
with current expert’s opinions. 21

Argatroban half-life after discontinuation

We found an argatroban plasma half-life of about 1 h
in patients with normal liver function (Figure 2A,B).
Accordingly, Figure 7 confirms that the decay of PAC after
argatroban discontinuation follows the same kinetics. We
therefore suggest discontinuing argatroban at least 2 h be-
fore any invasive intervention among patients with normal
liver function.

The effect of argatroban on the INR

As well as direct oral anticoagulants, 9 VKA are still employed
for HIT patients after the acute phase, 5 targeting INR values
between 2 and 3 for optimal anticoagulation. 5 Of note, ar-
gatroban and other direct thrombin inhibitors increase INR
values; this implies that during the overlap phase of anti-
coagulation with both argatroban and VKA, INR values greater
than 2–3 have to be achieved before stopping argatroban. 25
Harder et al. 26 recommend to target INR values higher than
4 and Bartholomew et al. 27 recommend performing INR con-
trols 6 h after argatroban discontinuation. In Figure 8, we
show that INR values ranging from 3.5 to 4.5 during the over-
lapping phase are sufficient to obtain a target INR of 2–3 after
argatroban discontinuation. Indeed, we observed a median
INR decrease of 1.2 (range: −0.7; −1.7) when control was per-
duced 3–6 h after argatroban discontinuation. These data
are perfectly in line with those obtained by two other groups
who observed median INR decreases of 1.2. 6,28

Limitations of our study

Our study has limitations. Firstly, this was a single-centre
study. Secondly, our data were collected retrospectively.
Thirdly, argatroban monitoring with a commercial di-
luted TT is not widely available. Nevertheless, all HIT
cases were confirmed by a functional gold standard assay,
we studied patients treated in a real-world clinical setting
and analysed an argatroban treatment length of 729 days.
Moreover, to the best of our knowledge, our cohort is the
biggest ever described including patients with HIT con-
ﬁrmed by a functional gold standard assay who were
treated with argatroban. 6,11,29–32

Practical implications of our study

Our results provide guidance on some practical aspects of an-
ticoagulation of HIT patients with argatroban, such as: (i)
the effect of various argatroban starting doses and dose ad-
justments on the following plasma concentrations; (ii) the
effect of liver function on argatroban dosing; (iii) the effect of tim-
ing and laboratory assay on monitoring; and (iv) the effect of
therapeutic argatroban on INR values. Based on these data we
have developed a standardised in-house management protocol (Table 5), which we are prospectively validating. Briefly, we do not differentiate between HIT and HIT-T and employ a SAD of 1.0 μg/kg/min in all HIT patients with normal liver function. In patients with impaired liver function, we decrease SAD to 0.75 μg/kg/min in presence of isolated hepatic cytolyis and to 0.25 μg/kg/min in case of hyperbilirubinaemia. We monitor treatment with a double pharmacokinetic and pharmacodynamic approach. On one side, we assess PAC at steady state employing a thrombin-time-based assay, which is more robust than aPTT. On the other side, we follow the course of platelet counts and D-dimer levels in order to fine-tune the anticoagulation intensity required in each individual patient.

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CONFLICT OF INTEREST

The authors do not have any conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Matteo Marchetti designed the research, collected and analysed data, and wrote the manuscript. Stefano Barelli designed the research and cowrote the manuscript. Tobias Gleich and Francisco J. Gomez collected data. Matthew Goodyer cowrote the manuscript. Francesco Grandoni was in charge of the patients, analysed data and cowrote the manuscript. Lorenzo Alberio is the corresponding author of the manuscript. He was in charge of the patients, designed the research, analysed data, and wrote the manuscript. All authors read and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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