

# The direct thrombin inhibitor argatroban: a review of its use in patients with and without HIT

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**Abstract:** Argatroban is a synthetic direct thrombin inhibitor with a relative short elimination half-life of 45 minutes and elimination which is predominantly performed via hepatic metabolism. Argatroban anticoagulation has been systematically studied in patients exhibiting the heparin-induced thrombocytopenia (HIT)/thrombosis syndrome and demonstrated to be a safe and effective therapy in this indication. Moreover, in smaller studies argatroban has also been assessed in special clinical settings in non-HIT patients. The current review presents the pharmacology of argatroban, data regarding monitoring of the agent, and an overview of the results of the major clinical trials assessing argatroban anticoagulation in HIT patients. Additionally, data from clinical trials with argatroban use outside HIT, in more special indications such as in percutaneous coronary intervention, stroke, renal replacement therapy, and intensive care medicine, are reviewed.

**Keywords:** anticoagulation, direct thrombin inhibitors, HIT

## Introduction

Heparins, particularly unfractionated heparins (UFH), have been the standard anticoagulants in nearly every field of anticoagulation therapy for decades. However, increasing recognition of the limitations of efficacy and safety of UFH therapy, particularly the hazard of heparin-induced thrombocytopenia (HIT), a severe disease in which heparin reverses its effect and may lead to thromboses, has promoted the development of new anticoagulants. The direct thrombin inhibitors (DTI), such as argatroban, bivalirudin, and lepirudin, are a class of potent anticoagulants that are playing an emerging role in modern anticoagulation therapy and are effective in the treatment of HIT-induced thromboembolism and as alternative anticoagulants for thrombosis prophylaxis in patients diagnosed for HIT. Furthermore, in special indications such as percutaneous coronary intervention (PCI), DTIs have demonstrated improved clinical results when compared with therapy with UFH (DTI Group). Argatroban, a small synthetic DTI, is the only alternative anticoagulant that in US jurisdiction is approved for both treatment of HIT-induced thromboembolism and prophylaxis of HIT. The current review presents the pharmacology of argatroban, an overview of the results of the major clinical trials assessing argatroban anticoagulation in HIT patients, and data from clinical trials with argatroban use outside HIT in more special indications such as in PCI, stroke, renal replacement therapy, and intensive care medicine.

## Pharmacology of argatroban

Argatroban is a synthetic monovalent direct thrombin inhibitor, the molecular structure of which contains an arginine residue. Argatroban is highly selective for thrombin and has little or no effect on related serine proteases (trypsin, factor Xa, plasmin, and kallikrein). Argatroban is effective against free, fibrin-bound and clot-bound thrombin with comparable half-maximal inhibitory concentrations (IC<sub>50</sub>), and

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argatroban is also effective in inhibiting platelet aggregation and thromboxane generation in the presence of both free and clot-bound thrombin. These pharmacologic properties are distinctly different from those of hirudin and heparin, for which markedly higher concentrations are required to inhibit clot bound thrombin in contrast to free thrombin (Berry et al 1994; Di Nisio et al 2005).

Argatroban is hepatically metabolized by hydroxylation and aromatization (mainly by CYP 3A4) to 4 main metabolites which do not possess relevant pharmacologic activity. Within a clinically relevant dose range (from 1–3 µg/kg/min in prevention or treatment of thrombotic events in HIT to up to 25 µg/kg/min in PCI in HIT patients), argatroban exhibits linear pharmacokinetic behavior, and steady state levels are attained within 1 hour after the start of an infusion. The elimination half-life of argatroban in healthy subjects is about 45 minutes, with a corresponding decline in its anticoagulant effects which reach their pretreatment level within 2–4 hours after cessation of an infusion. The pharmacokinetic profile can best be described by reference to a 2-compartment model with first-order elimination; effect response and plasma argatroban concentrations were well correlated (Swan and Hursting 2000). Argatroban lacks major drug–drug interactions with CYP3A4/5 inhibitors such as erythromycin (Tran et al 1999) or with acetaminophen, warfarin, and digoxin (Brown and Hursting 2002; Inglis et al 2002). There have been several studies which characterize the pharmacokinetic and pharmacodynamic properties of argatroban in vulnerable patient groups, ie, elderly patients and patients with renal and/or hepatic dysfunction. The only effect of age or gender was an approximately 20% lower clearance in elderly men versus elderly women, which does not translate into clinically or statistically significant differences in pharmacodynamic response (Swan and Hursting 2000). In patients with various degrees of renal dysfunction down to a creatinine clearance of 30 mL/min, no significant differences in the pharmacodynamic or pharmacokinetic profiles were detected (Swan and Hursting 2000). However, in patients with hepatic impairment, area under the concentration versus time curve (AUC), maximum concentration, and half-life of argatroban were increased approximately 2- to 3-fold, and clearance was one-fourth that of healthy volunteers. The increase in plasma concentrations in these patients coincided with increased pharmacodynamic effects (Swan and Hursting 2000). Dosing precautions are therefore recommended in patients with hepatic dysfunction, with reduced doses required particularly in patients with serum total bilirubin levels >25.5 µmol/L (1.5 mg/dL) or combined hepatic/renal

dysfunction (Levine et al 2006). It should be noted that, currently, no antidote to direct thrombin inhibitors is available.

## Monitoring of argatroban anticoagulation

Argatroban effects can be described using a variety of coagulation parameters, with a close dose/concentration vs effect relationship (Harder et al 2004). In most clinical studies, argatroban effects have been monitored by ACT (predominantly in high-dose therapy, eg, PCI setting) or aPTT (activated partial thromboplastin time) (in prevention/treatment of thrombosis in HIT). An infusion of 2 µg/kg/min argatroban is expected to increase aPTT 1.5-fold, whereas an infusion of 10 µg/kg/min can prolong a PTT up to 3-fold. In the PCI setting, the ACT is prolonged to 275–450 sec under 15–25 µg/kg/min argatroban (Yeh and Jang 2006). Although aPTT is an accepted coagulation parameter suitable to monitor argatroban in most clinical applications, its value has been challenged by the observation that the aPTT response to argatroban varies with the aPTT reagent, and approximately 1.5-fold differences in the prolongation of aPTT under the same concentration of argatroban have been observed between one reagent and another (Francis and Hursting 2005). In contrast, the ecarin clotting time (ECT) is a more specific monitoring parameter for direct thrombin inhibitors (Harder et al 2004), and a prolongation to 1.5- to 2-fold is attained by infusion of 2 µg/kg/min. However, assays vary considerably and unfortunately no point of care (POC) test for the ECT is commercially available.

Although not desired as a monitoring parameter, prothrombin time (PT) is also prolonged by argatroban, depending on the ISI of the PT reagent (Harder et al 2004). Argatroban furthermore decreases the endogenous thrombin potential in a dose/concentration dependent manner (Harder et al 2004).

## Transition from argatroban anticoagulation to oral anticoagulants

After intravenous anticoagulation, often transition to a prolonged period of oral anticoagulation with coumarin derivatives is necessary. The effectiveness and safety of therapy with coumarin derivatives are usually monitored using the PT expressed as the international normalized ratio (INR). Most publications related to warfarin suggest that an INR >4.0 is associated with an increased risk for bleeding complications (Bartholomew and Hursting 2005). All direct thrombin

inhibitors have an influence on the INR values, but this is particularly true of argatroban, presumably due to the high molar plasma concentration necessary to achieve effective thrombin inhibition (Warkentin et al 2005). This complicates the transition to oral anticoagulation when argatroban is used. Although no standard protocol exists, the most common procedure, which is included in the package advice, is to overlap with warfarin for a minimum of 4–5 days, aiming at an INR of  $>4$  (Harder et al 2004). Once this level is attained, argatroban therapy should be discontinued and testing of the INR repeated after approximately 6 hours to ensure that the therapeutic range is maintained (Bartholomew 2005). However, a retrospective analysis of the data of 111 patients from the ARG-911 and ARG-915 investigations who received argatroban/warfarin co-therapy and transition demonstrated that 5 (4.5%) patients experienced new thromboembolic complications during overlap at an INR value of  $>4$  but that only one patient (0.9%) experienced bleeding complications (Bartholomew and Hursting 2005). These data suggest that, particularly in patients with thrombotic HIT, during warfarin/argatroban co-therapy at an INR value of  $>4$ , the risk for thrombosis exceeds the risk for hemorrhage, so that in doubt higher INR values may be advisable in this special patient population. This suggestion is supported by other data from 165 HIT patients which demonstrated that INR values of  $>5$  during argatroban monotherapy and argatroban/warfarin combination therapy frequently occur without increasing the risk for major bleeding complications (Hursting et al 2005).

As discussed in the following sections, special patient populations, such as intensive care unit (ICU) patients and patients who have undergone cardiovascular surgery, reveal increased sensitivity to argatroban anticoagulation, thus requiring significant dose reductions. As particularly the molar concentration of argatroban appears to be responsible for interference with the INR, further studies should assess the extent to which the significant dose reduction in these patient populations also has implications for the effect of argatroban on the INR and the practice of transition to coumarin therapy.

## Argatroban anticoagulation in patients with HIT

### Argatroban anticoagulation in the treatment of acute HIT

In patients diagnosed for HIT, antibodies directed against the complex of heparin and platelet factor 4 (PF4) are generated.

The antigen/antibody complexes bind to the Fc receptor of platelets and induce platelet activation. Activated platelets on the one hand release PF4, thus causing increased formation of antigen/antibody complexes, and on the other hand cause the massive activation of thrombin, which is the most potent intrinsic activator of platelets. This massive generation of thrombin establishes a severe hypercoagulant condition that may finally lead to consumption of platelets and thrombin in thromboembolic events such as peripheral and mesenteric thrombosis and embolism, myocardial infarction, and stroke (Warkentin 2004a, b). The condition of HIT/HIT thrombosis syndrome (HIT(TS)) requires the immediate institution of alternative anticoagulation to prevent or treat these thromboembolic complications. As the “thrombin burst” plays a central role in this cascade of events, potent inhibition of thrombin action is the central therapeutic act in the treatment of the disease. As DTIs are among the most potent inhibitors of thrombin, this class of agents, particularly lepirudin and argatroban, has been intensively studied in this regard.

The safety and efficacy of argatroban anticoagulation for treatment of acute HIT(TS) has been assessed in two large prospective trials which were similar in their study design: the ARG-915 study and the ARG-911 study (Lewis et al 2001, 2003). Due to the lack of an approved competitor, the outcome of patients diagnosed for HIT and or thrombotic HIT and treated with argatroban was compared with that of an historical control group in which therapy followed the local departmental standards. Argatroban therapy was initiated with a continuous infusion of 2  $\mu\text{g}/\text{kg}/\text{min}$  which could be adjusted to a maximum of 10  $\mu\text{g}/\text{kg}/\text{min}$  in order to achieve a prolongation of the aPTT to a target value of 1.5–3 times of baseline but a maximum of 100 seconds. The prospectively defined primary endpoints of efficacy were the composite of death from all causes, all cause amputation and new thrombosis within 37 days. Among the safety endpoints the bleeding data were most important.

The efficacy and safety outcomes are presented in Tables 1 and 2. In both studies argatroban anticoagulation resulted in a significant reduction of the composite endpoint in the HIT population and a marked but not significant reduction of the composite endpoint in the HITTS population. Major bleeding complications were observed in 3%–6% of argatroban treated patients except for 11.1% in the HITTS population of the ARG-911 trial. These results were observed with a mean argatroban dose of  $1.7 \pm 1 \mu\text{g}/\text{kg}/\text{min}$  in the ARG 915 study and  $1.9\text{--}2.0 \pm 0.1 \mu\text{g}/\text{kg}/\text{min}$  in the ARG-911 study.

The direct thrombin inhibitor lepirudin, which is exclusively eliminated via the kidneys and has a longer plasma

**Table 1** Efficacy and safety outcomes in the ARG-911 trial

Outcome	HIT		p value	HITTS		p value
	Control (n = 147)	Argatroban (n = 160)		Control (n = 46)	Argatroban (n = 144)	
Composite end point	57 (38.8%)	41 (25.6%)	0.0014	26 (56.5%)	63 (43.8%)	0.131
Death	32 (21.8%)	27 (16.9%)	0.311	13 (28.3%)	26 (18.1%)	0.146
Amputation	3 (2%)	3 (1.9%)	1.000	4 (8.7%)	16 (11.1%)	0.787
New thrombosis	22 (15%)	11 (6.9%)	0.027	9 (19.6%)	21 (14.6%)	0.486
Major bleeding	12 (8.2%)	5 (3.1%)	0.078	1 (2.2%)	16 (11.1%)	0.077

**Abbreviations:** HIT, heparin-induced thrombocytopenia; HITTS, HIT/HIT thrombosis syndrome.

elimination half-life of 60–80 min, had been assessed for treatment of acute HIT(TS) (Greinacher et al 1999a, b). While clinical outcomes were comparable with the results obtained in the argatroban trials and demonstrated improved efficacy compared with the historical control groups, major bleeding events were observed in 12.9%–13.4% of patients.

A limitation of the argatroban/HIT trials must be noted that, in contrast to the studies with lepirudin where the diagnosis of HIT had to be proven in a functional washed platelet aggregation assay, in the ARG-911 and ARG 915 trials the diagnosis of HIT was only based on the absolute platelet count, or course of the platelet count and not confirmed in an antigen or functional HIT assay. Therefore patients may have been enrolled in this study who did not experience HIT but a decrease of the platelet count due to other comorbidities or medications.

### Argatroban anticoagulation during percutaneous coronary intervention

Three prospective studies, the ARG-216, ARG-310, and ARG-311 studies, have been performed to evaluate the safety and efficacy of argatroban anticoagulation during PCI [22]. Patients were followed during argatroban infusion and 24 hours after its cessation (or until hospital discharge) for the occurrence of death, emergency coronary artery bypass graft surgery, repeat PCI, myocardial infarction, and bleeding.

Argatroban was given with an initial bolus of 350 µg/kg (up to 3 additional boluses of 150 µg/kg were allowed) followed by a continuous infusion of 25 µg/kg/min (which could be adjusted to 15–40 µg/kg/min) in order to achieve a target activated clotting time (ACT) of 300–450 seconds during the intervention.

A total of 91 patients underwent 112 separate coronary interventions. The mean infusion dose of argatroban was 23 µg/kg/min; 25 patients received a second bolus of argatroban and 4 patients a third. Among all patients 92.3% remained free from all major acute complications and 97.7% achieved angiographic and clinical success. The overall incidence of death, myocardial infarction, or revascularization at 24 hours was 6.3% with an overall major bleeding rate of 0.9% (Lewis et al 2002).

### Argatroban in intensive care and cardiothoracic HIT patients

In the large ARG-911 and ARG-915 studies intravenous argatroban anticoagulation was started with a dose of 2 µg/kg/min and adjusted to achieve a target aPTT prolongation of 1.5–3 of baseline value with a maximum of 10 µg/kg/min and maximum aPTT value of 100 seconds (Lewis et al 2001, 2003). Even taking into consideration the large variability of the dose effect of argatroban on different aPTT reagents (Francis and Hursting 2005), both studies showed that the

**Table 2** Efficacy and safety outcomes in the ARG-915 trial

Outcome	HIT		p value	HITTS		p value
	Control (n = 139)	Argatroban (n = 189)		Control (n = 46)	Argatroban (n = 229)	
Composite end point	54 (38.8%)	53 (28%)	0.04	26 (56.5%)	95 (41.5%)	0.07
Death	29 (20.9%)	36 (19%)	0.78	13 (28.3%)	53 (23.1%)	0.45
Amputation	4 (2.9%)	8 (4.2%)	0.57	5 (10.9%)	34 (14.8%)	0.64
New thrombosis	32 (23%)	11 (5.8%)	<0.001	16 (34.8%)	30 (13.1%)	<0.001
Major bleeding	12 (8.6%)	10 (5.3%)	0.27	1 (2.2%)	14 (6.1%)	0.48

**Abbreviations:** HIT, heparin-induced thrombocytopenia; HITTS, HIT/HIT thrombosis syndrome.

anticoagulant effect was quickly achieved with a bolus and that minimal dose adjustments were necessary to maintain the aPTT within the target range. However, there are case reports of a dramatic overshoot of the aPTT with this standard dose when given to patients on the (ICU) or patients following cardiac surgery (Reichert et al 2003; Williamson et al 2004; Koster et al 2006; Beiderlinden et al 2007). In a recent investigation in critically ill patients with multiple organ dysfunction and suspected HIT, the dosing of argatroban had to be reduced to 0.2 µg/kg/min to avoid excessive anticoagulation and bleeding (Beiderlinden et al 2007).

First data of the European ARG-E03 study of patients having undergone cardiovascular surgery confirmed this observation (Koster et al 2006). In 18 of 20 patients after cardiovascular surgery the initial infusion dose was reduced to 1 µg/kg/min and in most patients the continuous infusion was further reduced to approximately 0.5 µg/kg/min during the further clinical course. This dose of 0.5 µg/kg/h was also confirmed to be the most appropriate in ICU patients with renal failure and liver dysfunction. These data suggest that there are significant differences in the susceptibility of special patient populations.

Argatroban has also been used for anticoagulation during cardiac surgery with and without cardiopulmonary bypass (CPB). However, to date no comprehensive dosing protocol for argatroban anticoagulation in these settings exists and both bleeding complications and thrombosis of CPB circuits have been observed (Monte et al 2007). Therefore, to date, the use of argatroban in this indication should be discouraged.

## **Argatroban anticoagulation in patients without HIT(TS)**

### **Argatroban anticoagulation during percutaneous coronary intervention and myocardial infarction**

An open label study enrolling 152 patients investigated argatroban anticoagulation in conjunction with a platelet glycoprotein IIb/IIIa (GP IIb/IIIa) antagonist during PCI (Jang et al 2004). Argatroban was given with a bolus of 250 or 300 µg/kg followed by an infusion of 15 µg/kg/min together with the GP IIb/IIIa antagonists eptifibatid or abx cimab to achieve a target ACT value of 275–325 seconds. Four patients (2.6%) suffered the primary endpoint of death, myocardial infarction or need for revascularization within 30 days. Major bleeding was observed in 2 (1.3%) of patients. The authors suggested that during elective PCI argatroban in conjunction with

a GP IIb/IIIa antagonists provides adequate anticoagulation with minor bleeding complications (Jang et al 1999).

In the MINT (Myocardial Infarction with Novastan and rTPA) study, the effect of argatroban and fibrinolytic therapy was compared to heparin plus fibrinolytic therapy in 125 patients with acute myocardial infarction (AMI) (La Monte et al 2004). Argatroban was given in a low dose with a 100 µg/kg bolus and infusion of 1 µg/kg/min (n = 38) or a high dose with the same bolus but an infusion of 3 µg/kg/min (n = 47) with recombinant tissue factor plasminogen activator (rTPA). These patients were compared with 40 patients with heparin and rTPA anticoagulation. The composite endpoint of death, recurrent myocardial infarction, cardiogenic shock or congestive heart failure, revascularization, and recurrent ischemia within 30 days occurred in 37.5% of heparin patients, 32% of low-dose argatroban patients, and 25.5% of high dose argatroban patients. Major bleeding was observed in 10% of heparin patients, 2.6% of low dose argatroban patients, and 4.3% of high dose argatroban patients (La Monte et al 2004). The authors concluded that argatroban together with rTPA appears to provide improved reperfusion after AMI when compared to heparin and rTPA.

## **Argatroban anticoagulation in acute ischemic stroke**

There are only a few small clinical pilot studies in which argatroban anticoagulation has been investigated outside the setting of HIT(TS). The ARGIS-1 study is a randomized, double blinded, placebo controlled study of the use of argatroban in acute ischemic stroke (Sugg et al 2006). In this investigation, 112 patients with acute ischemic stroke (<12 hours from onset) received argatroban at two different dosages (bolus 100 µg/kg followed by a continuous infusion of 3 µg/kg/min, n = 59 or 1 µg/kg/min, n = 58) to achieve target aPTT values of 2.25 and 1.75 of baseline value. The control group consisted of 54 patients. The primary endpoint was symptomatic intracranial hemorrhage (ICH) within 30 days. The mean infusion doses were 2.7 and 1.2 µg/kg/min for the high- and the low-dose groups, respectively. Target aPTT values were achieved within 2 hours after initiation of therapy. No major symptomatic hemorrhage was observed during the period of investigation and minor systemic hemorrhage increased only with high dose argatroban versus placebo (27.1% vs 11.1%). The 90-day mortality was 13.5% with no difference in survival rates between groups.

Preliminary results of 15 patients with acute stroke enrolled into the argatroban-rTPA study are available (Arpino and Hallisey 2004). In this investigation the dosing of the

lower-dose group of the ARGIS-1 study was combined with rTPA lysis. Primary outcome was incidence of ICH and secondary outcome complete re-canalization after 2 hours. Symptomatic ICH occurred in 2 patients and asymptomatic bleeding in 1 patient and there was 1 death. Complete re-canalization was achieved in 6 patients and partial re-canalization in 4 patients; re-occlusion occurred in 3 patients. The authors concluded that the safety profile of this protocol may be within acceptable limits and that its efficacy for achieving fast and complete re-canalization is promising, but that further data are needed.

## Argatroban for anticoagulation during renal replacement therapy

The half-life of argatroban is moderately extended in patients with renal insufficiency: At a creatinine clearance of 0–29 mL/min, the half-life of argatroban was  $64 \pm 35$  min versus  $47 \pm 22$  min at a creatinine clearance  $>80$  mL/min ( $p = 0.58$ ) (Swan and Hursting 2000). Even though a correlation of creatinine clearance and aPTT-adjusted argatroban dose has been described (Arpino and Hallisey 2004; Guzzi et al 2006), a recent retrospective analysis of multicenter trial data suggests this correlation not to be of clinical significance, and initial adaptation of the argatroban dose to renal function was regarded as unnecessary (Guzzi et al 2006).

Concerning intermittent hemodialysis (HD), a prospective crossover study of 13 maintenance HD patients showed 3 different argatroban dosing regimens (250  $\mu$ g/kg bolus alone, with an additional 250  $\mu$ g/kg bolus allowed; 250  $\mu$ g/kg bolus followed by 2  $\mu$ g/kg/min infusion, or 2  $\mu$ g/kg/min infusion at steady state with initiation of argatroban infusion 4 hours before dialysis) to be safe and well tolerated (Murray et al 2004). In a retrospective analysis of 47 patients with HIT and renal failure requiring renal replacement therapy, argatroban provided effective anticoagulation with an acceptable safety profile (Reddy et al 2005).

In ICU patients suffering from renal, but not measurable liver insufficiency, however, dose reductions may be frequently necessary (unpublished observations of the author). Based on this experience, in ICU patients we start argatroban at a reduced dose, provided there is no acute thrombosis. Careful monitoring and dosing are specifically required in this patient population. Similar experiences have also been reported by others (de Denus and Spinler 2003; Guzzi et al 2006). Here, decreased cardiac output or hepatic congestion has been discussed as causing reduced argatroban requirements (Guzzi et al 2006).

Whether anticoagulation with argatroban alone always prevents clotting in the extracorporeal circuit is unclear. In one HIT patient on HD treated with argatroban, marked spontaneous platelet aggregation occurred, perhaps due to HIT together with the additional platelet activation known to occur in HD (Koide et al 1995). In this case, aspirin was added to achieve patency of the extracorporeal circuit.

Dialytic argatroban clearance by high-flux hemodialyzer membranes is regarded as being clinically insignificant (Murray et al 2004; Tang et al 2005). However, as both low-flux and high-flux membranes show significant argatroban sieving (Krieger et al 2007), hemofiltration appears to be a suitable rescue measure if rapid removal of argatroban is required, eg, in the case of bleeding or accidental overdose, especially if hepatic clearance is reduced.

Its predominant hepatic elimination makes argatroban favorable for alternative anticoagulation in chronic renal failure. Its role and dosing in ICU patients suffering from acute renal failure requiring renal replacement therapy remain to be defined.

## Conclusion

Heparin-induced thrombocytopenia is a not infrequent, severe disease associated with potentially catastrophic thromboembolic complications. The data of the ARG-911 and ARG-915 investigations provide convincing evidence that argatroban enables rapid and effective anticoagulation in this condition and is an effective therapy for HIT-associated complications. Furthermore, in comparison with the direct competitor lepirudin, a DTI which is eliminated exclusively via the renal system, the safety margin of argatroban appears to be extended, as shown by the lower rate of major bleeding events than in the lepirudin studies.

Renal impairment with the need for renal replacement therapy is a frequent complication of HIT, especially in ICU patients. Particularly in this indication argatroban anticoagulation appears to be a very promising option. However, more investigations in this field are needed and reliable protocols for dosing should be established.

In the field of PCI in HIT patients data are less convincing and the optimal dose to prevent the frequent need of re-bolusing, for example, has not yet been established. Data obtained in this special indication with bivalirudin, another short-acting DTI that is emerging as a replacement for heparin in PCI, suggest a more constant dose–effect relation associated with a convincing efficacy and safety profile (Lincoff et al 2003; Mahaffey et al 2003; Stone et al 2006).

In the fields outside HIT, results obtained in patients with acute stroke are interesting and deserve further detailed

investigation. However, before data from larger studies are available all studies outside HIT have the character of pilot investigations. Moreover, special patient populations, particularly patients on the ICU, need further attention in order to establish reliable dosing schemes and protocols.

The practical problem of transition from argatroban anticoagulation to oral anticoagulants requires a standard protocol for the condition of HIT(TS) and in non-HIT patients. Use of more specific assays to monitor argatroban, such as the ECT, may be helpful in this regard.

We conclude that argatroban is a valuable drug for the condition of HIT(TS) that needs more detailed investigation in a large number of special indications and clinical settings.

## Disclosures

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