Appendix

Danaparoid: details on complication and outcomes. Bleeding complications were reported from 3 cases (fatal pulmonary hemorrhage after 8 days of therapy [32], non-fatal mediastinal bleeding after cardiac surgery with concomitant hepatic dysfunction and coagulopathy [28], bleeding from venipuncture sites under simultaneous tPA administration subsiding after stopping r-tPA [22]). In 1 patient, danaparoid was replaced by hirudin after 1 day due to in vitro cross reactivity between danaparoid and heparin [25]. Following the development of a new deep vein thrombosis on the 25th day of danaparoid therapy in another patient, in vivo cross reactivity was suspected, and danaparoid was replaced by lepirudin and phenprocoumon, resulting in full recovery [36]. In a neonate with HIT, danaparoid was changed to lepirudin because thrombocytopenia failed to resolve [43]. In 3 patients undergoing oral anticoagulation, overlapping danaparoid therapy was stopped after an INR 2-2.5 was reached [31,36]. In a preterm infant with solitary HIT, a low dose continuous infusion of 15 U/day in 150 ml resulted in a platelet count recovery and patency of the catheter [35].

Lepirudin: dosing and outcome of the 8 patients. A bolus of 0.4 mg kg\(^{-1}\) was only given to a 7 year old girl followed by continuous infusion of 0.15 mg kg\(^{-1}\) hour\(^{-1}\) [38]. In a neonate with thrombocytopenia, lower lepirudin doses were suggested: the target aPTT could be achieved after a bolus of 0.2 mg kg\(^{-1}\) followed by continuous infusion of 0.03-0.05 mg kg\(^{-1}\) hour\(^{-1}\) [43]. An 8 year old girl was treated with 0.15 - 0.16 mg kg\(^{-1}\) hour\(^{-1}\) for 2 days, during which oral anticoagulation with therapeutic INR could be installed [40]. An 11 year old girl was treated with a lepirudin dose between 0.15 to 0.22 mg kg\(^{-1}\) hour\(^{-1}\) [30,33,44]. A 15 year old boy was treated with 0.1-0.12 mg kg\(^{-1}\) hour\(^{-1}\) for 8 days [16]. A 2 day administration of lepirudin was reported by Zöhrer et al. [36]. All these patients were reported to have an
uneventful treatment. Schiffmann et al. reported a 12 year old boy receiving lepirudin for 2 months initiated with a bolus 0.2 mg kg\(^{-1}\) followed by continuous infusion of 0.1-0.7 mg kg\(^{-1}\) hour\(^{-1}\), according to aPTT values. This patient had to undergo limb amputation despite additional aggressive treatment with thrombolytic agents and arterial thrombectomy. Because of its low half-time in plasma the surgical procedure could be performed rapidly after temporary withdrawal of lepirudin. Lepirudin was stopped after oral anticoagulation resulted in a therapeutic INR [25]. Besides the latter patient, no other adverse effects were reported.

**Argatroban: details on the reported use in children.** Two neonates undergoing extracorporeal membrane oxigenation (ECMO) for diaphragmatic hernia were given argatroban at infusion rates of 0.5 to 10 µg kg\(^{-1}\) minute\(^{-1}\) to maintain an activated clotting time (ACT) of 200 sec for 6 and 78 days respectively [50]. In a 5 months old child suffering from HIT 14 days before cardiac catheterization, cardiac catheterization was uneventfully performed using the adult dosing scheme of a bolus (250 µg kg\(^{-1}\)) followed by continuous infusion of 15 µg kg\(^{-1}\) minute\(^{-1}\). Because of further planned cardiac surgery, a pre-operative pharmacokinetic study was performed. A bolus of 250 µg was given followed by continuous infusion of 10 µg kg\(^{-1}\) minute\(^{-1}\) resulting in therapeutic ACT and aPTT. There were no adverse effects reported using these dosing schemes [39].

**Special clinical situations:**

**Hemodialysis** with danaparoid proved safe in 2 patients using the following dosage: 1500 U plus 30 U kg\(^{-1}\) given as a single i.v. bolus at the start of hemodialysis. Dosage was adjusted according to the predialytic anti-factor Xa levels: <0.3U/mL (dose unchanged), 0.3-0.5 U/mL (total dose reduced by 250 U), >0.5 U/mL (no danaparoid). The average danaparoid dose per
hemodialysis session amounted 2'100 U in a 25kg 10 year old boy, and 3'000 U in a 35 kg 14.5 year old boy [34].

In a 6.8 kg 5 month old child with HIT following cardiac surgery, **cardiac catheterization** was accomplished with argatroban: a 250 µg kg⁻¹ danaparoid bolus followed by 15 µg kg⁻¹ minute⁻¹. This resulted in an ACT during catheterization of 315 sec [39]. In a 14 month old boy with body weight 9.2 kg, danaparoid was safely administered after HIT following cardiac surgery: an initial loading dose of 30U kg⁻¹ was followed by continuous infusion of 2 U kg⁻¹ hour⁻¹. After reaching an anti-factor Xa level of 1.3 U/mL during cardiac catheterization, the patient could be discharged without bleeding or thromboembolic complications [37].

A 4 year old girl with HIT was successfully treated with lepirudin and had to undergo subsequent **extracorporeal membrane oxygenation** (ECMO), which could be operated without thrombotic or hemorrhagic complication [38]. The loading and maintenance doses were calculated on the basis of the patient’s blood volume and the ECMO circuit volume. Estimated blood volume was 900mL (12 kg body weight and estimated 75 mL blood kg⁻¹). The loading dose of 0.4 mg lepirudin kg⁻¹ was translated into 0.4 mg per 75 mL blood volume. For priming the 700 mL ECMO circuit, the same per milliliter dose was used. Maintenance dose was adjusted to aPTT levels 1.5 to 2.5 the median normal value. This procedure allowed a safe anticoagulation with only minor bleeding and without thrombotic complications during 13 days. Despite its convenience, bedside testing of aPTT did not provide valuable information on anticoagulant effect of lepirudin. Therefore, centralized laboratory testing of aPTT, was employed and the use of Ecarin clotting time, if available, has been recommended for laboratory monitoring of lepirudin anticoagulation [38].

In a 14 year old boy with a need for cardiac surgery, danaparoid was administered in a bolus dose of 5000 U, resulting in an anti-factor Xa activity of 1.5 U/mL and an ACT of 200 seconds during cardiopulmonary bypass. Postoperative danaparoid levels were kept at 0.4-0.8 U/mL corresponding to infusion rates of 0.01 to 0.02 U kg⁻¹ minute⁻¹ [23]. A 2 year old girl
with bodyweight 12 kg was administered a loading dose of 750 U (62.3 U kg⁻¹) with 4 U/mL in the prime resulting in an anti-factor Xa level of 1.7 U/mL. After 40 minutes the anti-factor Xa level has declined to 0.7 U/mL and a further bolus of 1500 U was given, achieving an anti-factor Xa level of 2.5 U/mL. Postoperative dosing was 4 to 6 U kg⁻¹ day⁻¹ to maintain an anti-factor Xa level of 0.4-0.8 U/mL. These procedures provided a safe anticoagulation in both patients [28].