Annals of Clinical and Medical Case Reports[R] ISSN 2639-8109 | Volume 15

Research Article Open Access

Danaparoid Sodium (Orgaran®) – a Review of its Off-label Uses

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Received: 05 Jan 2026
Accepted: 25 Jan 2026
Published:10 Feb 2026
J Short Name: ACMCR

Keywords:

Danaparoid; Off-Label; Paediatrics; Pregnancy; Hepatic Thrombotic Disorders

Citation:

Harry Magnani, Danaparoid Sodium (Orgaran®) – a Review of its Off-label Uses. Ann Clin Med Case Rep® 2026; V15(1): 1-25

1. Abstract

Danaparoid use has also been reported for off-label clinical disorders in predominantly non-HIT adults, children and in pregnancy. Despite some being included in the contraindications and warnings against danaparoid use the encouraging treatment outcomes suggest new indications for its use. These include some states of intracerebral bleeding (e.g. in patients with COVID-19 patients and vaccination-induced thrombosis), for portal vein thrombosis (PVT) treatment in the presence of hepatic failure/cirrhosis, for prevention of chemotherapy-induced hepatic sinusoidal obstruction syndrome (SOS) and transplant-associated thrombotic microangiopathy (TA-TMA) in children undergoing haematogenous stem cell transplantation (HSCT), in pregnancies complicated by a history of repeated fetal loss, growth retardation or non-HIT coagulopathies and for peri-cesarian section thromboprophylaxis. This review of off-label treatment outcomes of danaparoid use also suggests that some would benefit more if the continuous presence of both the antithrombotic and immune-modulating effects of danaparoid were present together in the circulation at all times. This can only be achieved if danaparoid is administered as a continuous i.v. infusion. Studies to validate this approach and to find the optimal daily dosing intensity of danaparoid for some of the above indications are required.

2. Introduction

Danaparoid was discovered in 1977 and clinical development began in 1981. It is purified from porcine intestinal mucosa after all heparin chains have been removed, as a white to faint yellow powder. Its mixture of short chain linear glycosaminoglycuronans (GAGs) with a M Wave of 4500 Daltons (range 2500 – 10000 Daltons) [1] consists mainly of heparan sulphates (HS), of which about 4%, the HA-HS, has a high affinity for AT while the major component, NA-HS, has no affinity for AT. The remainder is dermatan sulfate (DS, about 12%) and a small percentage of chondroitin sulphates. The protective effects of danaparoid are highly dependent on the amount, chain length and correct weight/weight ratio of these HA-HS and the NA-HS subfractions. However, as a by-product of heparin isolation, they are sensitive to any changes designed to improve the quality or quantity of heparin. Thus, maintenance of danaparoid integrity is highly important because of its intimate relationship with both efficacy and safety in clinical practice.

3. Pharmacy and Compatibility

Danaparoid sodium dissolved in saline (pH 7) is presented as Orgaran® 0.6mL glass break-neck glass ampoules containing 750 anti-factor Xa units (750 U) with sodium bisulphite as preservative. It is intended for intermittent subcutaneous (s.c.) and intravenous (i.v.) injection or continuous i.v. infusion but must not be given intramuscularly.

3.1. Pharmacodynamics

Table 1 shows that the HA-HS and NA-HS contribute equally to thrombin generation inhibition (TGI), the principal antithrombotic action of danaparoid. The HA-HS and DS also contribute a minor indirect antithrombin action via AT and HCII [2] respectively. In animal models the benefit (antithrombotic effect)/safety (bleeding induction) profile was shown to be better than UFH and the first generation LMWHs [3].

Danaparoid pharmacology in summary shows that:

• routine clotting tests cannot be used for its monitoring

• danaparoid elimination as measured by the urinary appearance of anti-Xa activity, is predominantly, if not entirely, renal [5]. In renal failure patients its plasma anti-Xa activity half-life is prolonged by 30-100% [6, 7] but there is also evidence that at least

the HS-HA component is metabolised by endogenous heparinase[8] and/or heparanase activity[9]. Whether this also applies to the other effective components of danaparoid has not been investigated.

• danaparoid hardly affects platelet activity [2], hence clots are platelet rich and primary haemostasis remains intact,

• it does not cause the release of PF4 or bind to it [10, 11].

• It does not cross the guinea pig or human placenta [12, 13]

• is not secreted into breast milk in amounts that could pose a problem for the baby [14].

• it has no effect on euglobulin clot lysis or plasma levels of tissue plasminogen activator, α2-antiplasmin or release of fibrin degradation products or Fragments E and Bβ15-42 [15]. However, it appears to increase the pore size of fibrin gels suggesting that in-vivo it could facilitate thrombolysis [16, 17] by increasing clot permeability to plasmin.

• In-vitro danaparoid significantly attenuates inflammatory responses to various stimuli [18-22] and also uniquely amongst approved anticoagulants interferes in-vitro with the immune pathogenesis of HIT [23-25] and of VITT[26] by disrupting interactions of heparin and the HIT antibodies with their cellular and platelet targets. These actions, occur at therapeutic danaparoid dosing levels, and were considered to have significant implications for the treatment of DIC (particularly associated with sepsis) [22, 27-29], some auto-immune disorders and possibly infections such as COVID-19 [26,30, 31].

3.2. Pharmacokinetics

Table 1 illustrates the complex relationship between the components of danaparoid and their known effects. There is no single elimination half-life for danaparoid as such because it is a mixture of GAGs. Hence elimination half-lives are only available for the components that produce its pharmacological effects or by direct measurement of the isolated NA-HS after removal of the HA-HS subfraction by AT-binding affinity chromatography. Thus neither the anti-Xa activity nor anti-IIa activity or NA-HS, with half-lives of 24.5h, 4.3h and 3.5h respectively [32], reflect the clinically important antithrombotic half-life of danaparoid. However in animals the TGI half-life, which integrates the effects of danaparoid's active components on haemostasis (see Table 1), was shown to have about the same half-life as the antithrombotic half-life of intact danaparoid [2]. Hence it is assumed that this relationship is also true for humans in whom the half-life of TGI activity is 6.7h. This assumption of a shorter overall functional half-life for danaparoid as a whole compared to the anti-Xa activity half-life is supported by early dose-finding clinical studies showing that for DVT prophylaxis twice daily administration was significantly more effective than once daily dosing [33-35]. In addition bleeding or thrombotic events during treatment are generally not related to plasma anti-Xa activity levels.

Studies of patients in renal failure requiring extracorporeal support[6, 7] found a 30-100% prolongation of the plasma anti-Xa activity elimination rate, supporting the major role of the kidneys in at least the elimination of the HA-HS component from the plasma.

Pharmacokinetic studies almost exclusively in healthy Caucasian volunteers and patients showed no clinically important influence of administration route (subcutaneous or intravenous), dose-administered and subject age or gender [4]. Similar studies in healthy Japanese volunteers revealed a plasma anti-Xa activity of half-life of 21.7h [7] suggesting a minimal influence of race on the metabolism/elimination of danaparoid.

Table 1: Functional aspects of danaparoid constituents.

Functional component	Mass percent of danaparoid	Clotting Cascade Action	Effect	Half-life of the Effect[1]	Contribution to antithrombotic activity
DS	~12%	Indirect anti-IIa activity via HCoII	Thrombin inhibition	4.3 hours	Minor
HA-HS	~4%	Indirect anti-IIa activity via AT			Minor
		Indirect anti-Xa activity via AT	Thrombin generation inhibition (TGI)	6.7 hours	Approximately 50%
NA-HS	~80%	Direct inhibition of thrombin activated FIXa generation			Approximately 50%
		Attenuates release of systemic inflammatory markers,	Immune-modulatory	No data	Possibly indirect
		Interferes with antibody interactions	Anti-inflammatory		
CS	~4%	None	None		None

[1]the half-life of the anti-Xa activity is 24.5 hours. The half-life of the NA-HS is 3.5 hours but the half-life of its effects on the immune system have not been studied.

3.3. General Dosing Regimens

Danaparoid was approved in Europe and Australia/New Zealand for DVT prophylaxis in orthopedic surgery in 1997, for HIT treatment in 1994 and in 2000 for DIC in Japan only. Since then it has also been used in various off-label clinical disorders.

Danaparoid dosing schedules for its approved indications were developed based on extensive experience in both non-HIT and HIT patients and pharmacokinetic modelling. The distinct dosing regimens for danaparoid shown in Table 2, taken from a recent consensus dosing recommendation [4], are for guidance only.

These limitations provide more detail for individual clinical scenarios and stress the importance of both dosing intensity and administration route, particularly when needed for therapeutic management. Underdosing appears to be an important cause of danaparoid treatment failures. Hence it is very important to follow these recommended treatment schedules unless the clinical status of a patient dictates otherwise. Particularly the loading i.v. bolus preceding therapeutic infusions, that allows immediate achievement of the desired plasma anti-Xa activity range after treatment initiation, should only be reduced or omitted if the patient has a high bleeding risk. Danaparoid antidote.

Animal and clinical models associated with a high bleeding risk support the safety profile of danaparoid [2] and overdosing, deliberate or accidental did not induce bleeding (a 12 month old boy with moyamoya disease received danaparoid 350 U/Kg/day for 10 days and 15 days on 2 separate occasions [36], i.e. 5 times the adult daily therapeutic dose, without incident. However, there are reports of severe haemorrhage during high-dose danaparoid use to protect cardio-pulmonary by-pass circuits in which plasma anti-Xa levels and bleeding failed to respond to products that reverse the heparins, i.e. protamine sulphate, DDAVP, EACA etc. [37]. It is possible that these bleeding events are related to the ability of danaparoid to increase clot permeability to thrombolytic activity [16, 17]. In some case reports bleeding was prevented using topical fibrin sealant/bone wax [38, 39] or aprotinin[40]. In addition, plasmapheresis [41], by effectively removing danaparoid (anti-Xa activity) over a 4-6 h period, also successfully controlled bleeding, and multiple transfusion[37] of blood products, e.g. fresh frozen plasma, slowly reduce bleeding over a 12-24 h period by blood dilution and possibly increased renal elimination of danaparoid. More recently a dose of 90 mcg/kg IV has been proposed for rFVIIa use [42] and in-vitro studies have suggested that rFVIII might also be effective [17]

Table 2: Danaparoid treatment regimens.

Clinical purpose	**Treatment schedule**	**Regimen**[2]
Medical Prophylaxis for Non-HIT & Remote HIT[1] **patients**	≤90 kg: 750 U b.i.d, s.c.	**1a**
	>90 kg: 750 U t.i.d. or 1250 U b.i.d., s.c.	
	Between days 7 to14 the transition to a VKA can be made	
Peri-operative TE prophylaxis in Non-vascular surgery for Non-HIT and HIT patients		**1b**
Pre-operative		
	Patient is already on a danaparoid therapeutic infusion and needs emergency surgery for which danaparoid will be used	
	Stop the infusion 12 h prior to surgery and give no further danaparoid pre-operatively	
	or	
	Patient is not already on danaparoid treatment or is on prophylactic danaparoid prior to surgery,	
	i.e.	
	≤90 kg: 750 U b.i.d, s.c. or	
	>90 kg: 750 U t.i.d. or 1250 U b.i.d., s.c.	
	Then give the last or only pre-op dose ≥6 hours prior to surgery.	
	The first post-operative dose when haemostasis is established but no earlier than 6 hours post-op.	
Post-operative	≤90 kg: 750 U b.i.d, s.c. for up to 14 days	
	>90 kg: 750 U t.i.d. or 1250 U b.i.d., s.c. for up to 14 days	
	If danaparoid is (still) required at therapeutic dosing levels post-operatively, then restart the infusion at the pre-operative maintenance infusion rate without a loading bolus when haemostasis is achieved but no sooner than 6 hours post-operatively' (see below [Regimen 2a] for maintenance infusion adjustments).	

Therapeutic dosing for Acute HIT and for CRRT use in the absence of clotting in Non-HIT or HIT patients	i.v. loading bolus as follows injected over 5-10 seconds:	**2a**
	2250 U i.v. for patients 55 – 90 Kg body weight,	
	1500 U i.v. for patients <55 kg body weight,	
	3750 U i.v. for patients >90 kg body weight,	
	Plus in all patients an immediate 'step-down' i.v. infusion of 400 U/h for 4h, then 300 U/h for 4h + then 150-200 U/h maintenance infusion for 7 days or longer if required.	
	NB In patients with impaired renal function (i.e. eGFR<30 mL/min/1.73m2) the maintenance dose should be reduced to 150 U/h.	
	The maintenance infusion rate can be adjusted according to the risk of bleeding. If monitored at steady-state within 6 hours of starting it the plasma anti-Xa activity level should not exceed 0.8 U/mL or be below 0.4 U/mL. If the plasma anti-Xa level is outside these levels or, in the absence of monitoring, thrombosis or bleeding occur then the maintenance infusion rate can be increased or decreased by increments of 20%.	
CRRT use if clotting is occurring, in Non-HIT and HIT patients	2250 U i.v. bolus, + step-down i.v. infusion of 400-600 U/h for 4h, then 300 U/h for 4h + then 100 - 400 U/h (maintenance rate)[3]	**2b**
	The aim is to reach the lowest rate that achieves and maintains circuit patency. High infusion rates within the range may be initially required if circuit clotting has been a problem or the patient recently received a high heparin dose. Once under control, the rate can be adjusted as indicated above for Regimen 2a depending upon whether it is only needed to maintain circuit patency or to provide systemic TE prophylaxis or treatment in a patient at high risk or affected.	
Vascular surgery/invasive vascular procedure in Non-HIT and HIT patients[4]		**3**
Pre-operative/procedure		
	≤90 kg: 2250 U i.v. bolus pre-procedure/surgery	**(2a)**
Intra-operative/procedure	>90 kg: 3750 U i.v. bolus	

3.4. Off-Label Treatment and Investigations

Many of danaparoid's off-label indications are related to the warnings and contraindications imposed on danaparoid at the time of its marketing approval for routine DVT prophylaxis use.

3.5. Danaparoid Contraindications

• hemorrhagic cerebrovascular accident within the previous three months,

• uncontrollable active bleeding state,

• severe, uncontrolled hypertension,

• diabetic retinopathy,

• hepatic jaundice accompanied by a prothrombin time >1.3 times normal,

• acute bacterial endocarditis

• a need for locoregional anesthesia particularly if therapeutic dosing is required,

• damage to the central nervous system or brain, spinal or ophthalmological surgery.

3.6. Danaparoid Warnings

• danaparoid should not be used if an in vitro test for the heparin-induced antibody in the presence of danaparoid is positive in patients with thrombocytopenia induced by heparin or heparin-like anticoagulants, unless no suitable alternative antithrombotic treatment is available,

• danaparoid should not be administered to patients with severe hemorrhagic diathesis, e.g. hemophilia and idiopathic thrombocytopenic purpura, unless the patient also has HIT and no suitable alternative antithrombotic treatment is available.

• danaparoid should not be used in patients with severe renal and hepatic insufficiency, unless the patient also has HIT and no alternative treatment is available.

• danaparoid should not be administered to patients with active gastric or duodenal ulceration, unless it is the reason for operation,

• danaparoid should not be used in pregnancy or in children unless the subject has HIT or another form of heparin intolerance,

• danaparoid should be used with caution in patients with moderately impaired renal and/or liver function with impaired hemostasis, ulcerative lesions of the gastro-intestinal tract or other diseases which may lead to an increased danger of hemorrhage into a vital organ or site.

• danaparoid contains sodium sulfite. In asthma patients hypersensitive to sulfite the latter can result in bronchospasm and/or anaphylactic shock.

These protections were based principally on too little information on danaparoid at the time of approval despite no events reported and/or serious adverse experiences with other antithrombotics. However, because of its general safety record danaparoid has been increasingly investigated in off-label indications for which the heparins are considered a bleeding risk or inadequately effective.

Although danaparoid use in pregnancy and for children was initially approved only for subjects with acute or remote HIT most experience has been in non-HIT off-label use.

3.7. Paediatric Treatment

Case reports are available for 476 danaparoid treatment episodes in 446 children (i.e. 30 children received two distinct episodes of treatment) aged 12 days to 18 years (age distribution in supplementary data but precise age only known for 91 patients). The first 34 children were previously reviewed [43]. Table 3 shows that off-label danaparoid was administered in 423 treatment episodes (for 395 non-HIT children) and 53 treatment episodes (49 acute, 3 remote and 1 suspected) in 51 children with HIT. The non-HIT indications were predominantly prophylaxis of sinusoidal obstruction syndrome (SOS) and transplant associated thrombotic microangiopathy (TA-TMA) following chemotherapy for haematogenous stem cell transplantation (HSCT) in children with mainly haematogenous cancers.

Table 4 summarises the recommended paediatric dosing schedules for the known indications for danaparoid treatment based on recommendations and clinical reports [43-48]. The ranges take into account the need to individually balance the risks of thrombosis and bleeding while attempting to achieve a plasma anti-Xa activity within the target range. Monitoring is initially recommended to avoid accumulation, but can be reduced once the desired plasma anti-Xa activity is steady for 2 consecutive days. However no plasma anti-Xa activity levels were reported for any of the Japanese children exposed to danaparoid. The most frequently reported clinical outcome parameters of danaparoid treatment (not available from all reports) are summarised in Table 5. The differences for new/persistent PCR and death due to haemorrhage between HIT and non-HIT outcomes are statistically significant ($p = 0.0013$ and 0.0127 respectively). The relatively high thrombosis rate (8.3%) in non-HIT subjects were almost all due to SOS, TA-TMA and graft host disease after HSCT. The 5 thrombosis-related events (9.6%) in HIT subjects occurred after danaparoid treatment initiation but include one occurred after concomitant heparin flushes and another was amputation of toes that were non-viable before danaparoid was started.

During the 450 reported paediatric exposures to danaparoid sodium there were 7 major bleeding episodes (1.6%) [43, 48-50], 2 of which, in infants with HIT, were fatal [43, 51]. These are described in detail in the supplementary data. A comparison of danaparoid plus ursodeoxycholic acid (UDCA) and dalteparin plus UDCA for the prevention of (hepatic) sinusoidal obstruction syndrome (SOS) and transplant-associated thrombotic microangiopathy (TA-TMA) after haematogenous stem-cell transplantation (HSCT) [48] found that treatment (chemotherapy) related mortality was significantly reduced (HR 0.019, $p<0.001$) in danaparoid treated subjects. A small post hepatic transplant comparison of danaparoid alone and UFH with a serine protease inhibitor [52] found no thromboses, bleeding or transplant rejection in the danaparoid group but rates of 21.2%, 15.2% and 12.1% in the heparin/serine protease group.

Table 3: Paediatric morbidity and reasons for danaparoid use.

	HIT		**Non-HIT (Off-label)**	
No. of treatment episodes	53	11.10%	423	88.9%*
Systemic TE/ECC circuit clotting	35	66.00%	6	1.4%*
Hereditary or acquired thrombophilia[1]	21	22.60%	58	13.7%*
Severe infection/sepsis	9	17.00%	7	1.7%*
DIC	1	1.90%	42	9.90%
Cancer (mainly haematogenous)[2]	1	1.90%	301	71.2%*
At least 1 organ failure[3]	16	30.20%	7	1.7%*
Admission bleeding	6	11.30%	3	3.7%*
Recent major surgery	204	37.70%	154	3.5%*
Neurological/Intracranial disorders[5]	5	9.40%	13	3.1%**
Scalding/3rd degree burns	2	3.80%	1	0.2%**
Required for major surgery	5	9.40%	0	0.0%*

Required for SOS/TA-TMA prevention post HSCT	1	1.90%	346	81.8%*
Required to maintain renal ECC patency	7	13.20%	1	0.2%*
Required for thrombosis prophylaxis - total	25	47.20%	363	85.8%*
Required for thrombosis treatment - total	33	62.30%	13	3.1%*

DIC=disseminated intravascular coagulation; ECC = extracorporeal circulation, HIT=heparin-induced thrombocytopenia; HSCT = haematogenous bone marrow transplantation, SOS = sinusoidal obstruction syndrome, TA-TMA = transplant associated thrombotic microangiopathy.

1 AT or PC or PS deficiency, Factor VII deficiency, Factor V Leiden, increased Factor VIII, G20210Ah anomaly, but not including chemotherapy treatment,

2 includes HSCT for a small unknown number of solid tumours,

3 mainly renal or hepatic failure but also some respiratory and cardiac failure and 1 child with MODS,

4 for HIT subjects predominantly CPBS , general surgery including appendectomy, multiple accident fractures, renal transplant, and SVC thrombectomy, and for non-HIT subjects hepatic transplant (8), Rex by-pass (6) and craniotomy,

5 subdural haematoma, diabetes insipidus, brain herniation, adrenoleukodystrophy, seizures, cerebrovascular malformation, CVA, SSST, GM-1 gangliosidosis.

In Table 3 the differences between HIT and non-HIT statistically significant (Fisher's exact test) *p = <0.0001, **p = <0.05.

Table 4: Dosing Schedules for Danaparoid Pediatric use.

Treatment Indication	**Age (years)**	Daily Dosing1 according to the target plasma anti-Xa activity response	**Target Plasma Anti-Xa-Activity**
	≤ 2	10 – 15 U/Kg b.d., s.c.	0.1 – 0.4 U/ml
Arterial and Venous Thromboprophylaxis			
	9 – 17	10 – 30 U/Kg b.d., s.c.	0.1 – 0.4 U/ml
SOS/TA-TMA prophylaxis post HSCT	1 – 18	15 – 30 U/Kg b.d., s.c. or i.v.	0.4 - 0.8 U/ml
	≤ 2	30 U/Kg i.v. loading bolus then 6 U/Kg/h i.v. infusion x 4h to maximum 300 U/h then 4 U/Kg/h i.v. infusion x 4h to maximum 200 U/h then a maintenance infusion 2.5 U/Kg/h	
General ThrombosisTreatment			0.4 – 0.8 U/ml
	9 – 17	30 U/Kg i.v. loading bolus to maximum 2250 U then 6 U/Kg/h i.v. infusion x 4h to maximum 400 U/h then 4 U/kg/h i.v. infusion x 4h to maximum 300 U/h then a maintenance infusion 3 U/Kg/h to maximum of 3000 U/day (but if >55 Kg then up to maximum 4800 U/day)	
Pre-Cardiac catheterization	≤ 2	60 – 120 U/Kg i.v.b. to maximum 1500 U	0.4 – 0.8 U/ml post bolus
Intermittent (not daily) haemodialysis	2 – 10	1st and 2nd dialysis: a pre-dialysis i.v. bolus 30 U/kg + 1000 U to a maximum of 2250 U/dialysis.	
	10 – 17	1st and 2nd dialysis: a pre-dialysis i.v. bolus 30 U/kg + 1500 U to maximum of 3000 U/dialysis	0.4 – 0.8 U/ml during dialysis

Table 5: Dosing Schedules for Danaparoid Paediatric use.

Continuous ambulatory peritoneal dialysis	≤ 2 – 17	5 – 15 U/Kg either s.c.in divided doses or as an i.v. infusion (0.2 – 0.6 U/Kg/h) to maximum 1000 U/day	insufficient data
	≤ 2	Post thoracotomy 1500 U i.v.b. CPB Priming fluid 4 U/mL	0.8 – 2.0 U/ml
Cardiac surgery			intraoperative
	7 – 17	Post-thoracotomy 5000 U i.v.b. CPB Priming fluid 5000 U total	0.8 – 2.0 U/ml intraoperative

3.8. Pregnancy and Lactation

Because danaparoid does not cross the placenta and is safe during breast feeding it was approved for use in pregnancies associated with HIT. To date 197 women are reported to have been exposed to danaparoid for 206 pregnancies (208 babies). The first 91 pregnancies have been previously reviewed [13, 14]. Danaparoid treatment was initiated in the first, second and third trimesters in 67.0%, 16.5% and 16.5% respectively. Tables 6 and 7 show the clinical problems (see also the supplementary data) at presentation and the treatment schedules used to treat them based on each patient's thrombotic/bleeding risk independent of HIT status.

Treatment duration during the 147 pregnancies with information was a median 14 weeks (range <1-39 weeks). Forty-seven subjects received continuous exposure for ≥ 30 weeks and for 2 of these danaparoid was started prior to the first positive pregnancy test and continued to term. During individual patient use the danaparoid dosing regimen was often adapted to changes in the individual clinical status, e.g.

• the thrombotic risk was under control, hence danaparoid was occasionally stopped or the dosing intensity reduced, if necessary a continuous i.v. infusion was reduced to s.c. prophylaxis,

• a TE occurred because of initial under-dosing (s.c. prophylaxis) and was increased either subcutaneously or to a therapeutic continuous i.v. infusion,

• the dosing intensity for restarting danaparoid post-partum was increased or lowered according to the patient's TE risk.

Finally, many subjects were taught to self inject danaparoid for home treatment both during and after birth.

For 3 current HIT and 22 non-HIT pregnancies there is no birth information since danaparoid was discontinued early either because it was no longer needed after successful treatment (n = 14) or because an adverse event occurred (usually recurrent skin reaction) for which it was switched to another antithrombotic. Table 8 summarises the known pregancy outcomes with danaparoid.

Three premature infants developed IRDS and 2 of these, delivered at 23 and 29 weeks, suffered a fatal pulmonary haemorrhage 2 and 4 days respectively after birth. All other prems developed normally. The less favorable birth rates in past and non-HIT patients were directly related to the number of prior early pregnancy losses. However 50-70% was demonstrated in 10 of the 26 early aborted fetuses in danaparoid treated subjects with obstetric antiphospholipid syndrome [55, 56], but if investigated in the other 16 aborted fetuses it was not reported. Three of the 10 were from consecutive danaparoid treated pregnancies in a woman with homozygous FVL anomaly, whose 4th and 5th pregnancies with danaparoid were successful [55]. Taking this into account the adjusted overall live birth rate is 87.7% (150/171).

Table 6: Outcomes of Paediatric Treatment with Danaparoid.

	HIT		Non-HIT	
N treatment episodes[1]	53	12.10%	423	87.90%
Recovered without problem	44	83.00%	341	80.60%
Total mortality[2]	4	7.50%	10	2.40%
TE Fatal	1	1.90%	0	--
MB Fatal	2	3.80%	0	--
Non TE/MB deaths	1	1.90%	10	2.40%
TE Non-fatal[3]	4	7.50%	35	8.30%
MB Non-fatal	2	3.80%	3	0.70%
Minor bleeding episode	1	1.90%	2	0.50%
New/persistent PCR	3	5.70%	0	--
Other adverse events	4	7.50%	15	3.50%

HIT=heparin-induced thrombocytopenia; incl.=including; MB=Major Bleeding; n/p PCR=new/persistent platelet count reduction; TE=thromboembolism

1 not all reports included specific treatment outcomes for danaparoid

2 All-cause mortality within 6 weeks of danaparoid discontinuation,

3 includes DVT and thrombotic syndromes for non-HIT subjects: SOS, TA-TMA, graft v host disorder.

Table 7: Presenting characteristics of Pregnancies exposed to danaparoid.

Presenting demographics	**Current HIT[1]**	**Past HIT[1]**	**Non HIT[1]**
Number of pregnancies	39	21	145
Age[2] (years) mean (range)	31.4 (20 – 42)	29.8 (23 – 40)	32.0 (19 – 42)
Thrombo-embolism[3]	34 87.2%	15 71.4%	35 24.1%
Active bleeding	1 2.6%	1 4.8%	4 2.8%
Skin rash	1 2.6%	0	32 22.1%
Skin necrosis	2 5.1%	1 4.8%	1 0.7%
Additional clinical problems4,5	9 25.7%	2 20.5%	10 7.0%
Thrombophilic problem[5,6]	22 66.7%	15 78.9%	105 73.9%
Repeated pregnancy loss[7]	3 7.7%	7 33.3%	73 50.3%
Pregnancies with ≥3 clinical problems	22 66.7%	2 20.5%	12 8.3%

[1]percentages based on the number of pregnancies
[2]for 23 -patients the age is unknown
[3] TE acute, recent, previous pregnancy or PP,
[4]cardiac anomaly (septal defects, artificial heart vales, fontan circulation), PES, Crohn's disease, pituitary [5] adenoma, Widal's disease, SBE, RTA, obesity, twins, cardiac shock, cardiac failure, renal failure, KMS),
[5]for 4 current HIT and 3 non-HIT pregnancies no data available,
[6] hereditary or acquired thrombophilia (clotting factor deficiency or abnormality, APS, PNH, DIC, T/ITP)
[7] ≥3 early foetal deaths with 1 or no live births.

Table 8: Danaparoid Dosing in Pregnancy.

Orgaran® use Daily dose given either i.v. and/or s.c	Pregnancy ± PP[1]	Peri and post- partum only[1,2]
N	179	290
≤2250 U s.c., b.d. or t.d.s:		
thrombosis prophylaxis	79 43.8%	145 50.0%
thrombosis/DIC treatment	15 8.4%	2 0.7%
>2250 U usually as i.v. infusion[3]:		
thrombosis prophylaxis	47 (1)[4] 26.4%	133 45.9%
thrombosis/DIC treatment	38 (17)[4] 21.3%	10 3.4%
Duration during pregnancy & delivery (weeks):		
median	14	1
range	<1 – 39	1 – 3
Duration post-partum (days):		
median	9.5	2
range	2 – 63	1 – 60

[1]only subjects with danaparoid treatment data
[2]not used during pregnancy, some women received 1 dose pre-CS
[2]in some patients large (up to 2000 U) s.c. doses were administered b.d. or t.d.s.
[4](in brackets) = danaparoid regimen initiated with an i.v. loading bolus.

3.9. Maternal Adverse Events

Adverse events reported during pregnancy or immediately after birth are summarised in Table 9. Of the 2 fatalities, one followed a post-partum haemorrhage from an abruptio placenta in a Jehovah's Witness patient who refused transfusion, the other followed an emergency cesarian section for a haemorrhaging placenta praevia after which the mother could not be resuscitated (autopsy revealed an unsuspected ASD and acute lung injury). There were 3 non-fatal major events: one a PPH that occurred when dextran was co-medicated with danaparoid for delivery (danaparoid was restarted post-partum once haemostasis was re-established), one occurred during emergency cesarian section for a placenta praevia that had already bled prior to danaparoid initiation and one occurred 7 days after danaparoid discontinuation due to uterine atony following UFH use for delivery. Ten minor bleeds were reported: 4 wound haematomas, 2 injection site bruises and 4 unspecified bleeding events [13] but for none was danaparoid treatment discontinued.

Not included in the table are 4 additional VTEs that responded favorably to increasing the danaparoid dosing intensity (one with aspirin and another with warfarin) and 11 bleeding events (mainly local haematomas or injection site bleeding, that responded to danaparoid continuation after dose reduction.

Skin rashes recurred in 17 of the 36 women presenting with a rash. In 3 of these continuing s.c. danaparoid injections led to tolerance, i.e. the diminishing rash ceased to recur after 5-7 days. However, for the remaining 14 subjects danaparoid was immediately discontinued, hence the frequency of danaparoid-mediated tolerance is unknown.

Table 9: Overall summary of Pregnancy outcomes.

Pregnancy outcomes	**Current HIT**	**Past HIT**	**Non-HIT**
	n = 39 (36)[1,3]	**n = 21**	**n = 145 (123)[1,3]**
Live Births:			
delivery at ≥37 weeks gestation[2]	29 80.6%	11 50.0%	84 68.3%
premature <37 weeks gestation	6 16.7%	5 22.7%	15 12.2%
total births	35 97.2%	16 72.7%	99 80.5%
Fetal loss ≤20 weeks gestation	0	6 27.3%	20 16.3%
Medical termination/stillborn[3]	1 2.8%	0	4 3.3%
Fetuses with chromosome aberration	0	3	7
Adjusted live births[4]	35/36 97.2%	16/19 84.2%	99/116 85.3%

[1]figures in brackets are the number of pregnancies with known birth outcomes.

[2]including a patient whose danaparoid was discontinued 5 days before expected delivery

[3]percentages of those with known outcome

[4]excluding pregnancies resulting in early fetal loss due to chromosome aberration.

Table 10: Serious1 Maternal adverse events during danaparoid exposure in pregnancy.

Maternal Adverse (AE) Events	**Current HIT**	**Past HIT**	**Non-HIT**
	n = 39	**n = 21**	**n = 145**
New thrombosis	5.1% 2	0	0
Major haemorrhage	7.7% 3	4.8% 1	0.7% 1
Isolated Thrombocytopenia	2.6% 1	0	0
Skin rash (recurrence)[3]	2.6% 1	4.8% 1	8.3% 12
Pre-eclampsia syndrome	7.7% 3	4.8% 1	4.1% 6
Cardiac dysfunction	5.1% 2	0	0
Renal dysfunction	0	0	1.4% 2
AST/ALT raised	0	4.8% 1	1.4% 2
Oligohydramnios	0	4.8% 1	0.7% 1
SLE reactivation	0	4.8% 1	1.4% 1
Vaso-vagal reaction	0	0	0.7% 1
Danaparoid resistance	0	0	0.7% 1
Maternal deaths	5.1% 2	0	0
Pregnancies with 1 or more AE	30.8% 12	23.8% 1	17.9% 1

3.10. Post-partum Danaparoid Use

The main reason reported for PP continuaton of danaparoid was a raised thrombotic risk, e.g. a history of thrombosis, obesity, DIC, HIT, ITP, SLE/APS, pre-eclamptic syndrome or clotting factor anomaly. Pregnancy use of danaparoid was continued as DVT prophylaxis for 28 routine, and 9 emergency cesarian sections (CS). After 21 of these operations it was reported to have been continued further and it was also re-started after vaginal delivery in 38 women. Specific administration data for 43 of these 59 subjects shows that danaparoid was used post-partum (PP) for a median 9.5 days (range 2 - 63 days). Post-partum danaparoid dosing was mainly 1250 U i.v. twice daily. In the total 315 patients undergoing cesarian section 6 (2.1%) major bleeding events were reported, including a fatal intracranial haemorrhage in a woman with an A-V malformation that had bled prior to danaparoid exposure, and an intraoperative haemorrhage in a subject with an unsuspected placenta praevia who was also taking diclofenac and a haemorrhage into the amniotic fluid. Thirteen surgical-site haematomas were reported and danaparoid was continued once these were controlled. There was 1 new DVT (0.4%) that resolved after danaparoid replacement with a VKA.

Table 11 summarises the pooled results of 2 retrospective comparisons of danaparoid vs heparin [59] and vs heparin and no antithrombotic [60] in patients undergoing cesarian section. With danaparoid there was an increased total peri-operative blood-loss but no adverse consequences were reported and danaparoid thrombosis markers normalised faster post-operatively.

Danaparoid was specifically requested during breast-feeding for at least 10 subjects. The amount of anti-Xa activity found in 6 mothers' breast milk samples was negligible and not considered a danger to the baby [14].

The relatively high frequency of maternal adverse events reflects the serious presenting clinical state of the subjects. Apart from the thrombotic, bleeding, skin rash recurrence and some PES danaparoid treatment was continued through the other events listed in Table 9. Thus, although danaparoid is associated with an unexplained increase in premature (but first live) births, it appears to be a safe and effective anticoagulant for pregnancy, CS and during breast feeding despite severe co-morbidity.

Table 11: Pooled results from two historic comparisons of danaparoid for post-CS DVT prophylaxis.

Treatment outcomes	Danaparoid n = 162	Heparin/LMWH n = 55	No antithrombotic[1] n = 124
Dose regimen	1250 U b.d., i.v.	5,000 IU b.d., i.v.[2]	--
Mean total blood loss[3,4]	989 ml	696 ml	nd
Post-operative VTE[5]	0	2 3.6%	1 0.8%
Post-operative haematoma	1 0.6%	3 5.4%	0

[1]these were patients with the lowest thrombotic risk

[2]the 4 dalteparin subjects received 5000 U

[3]available from 1 study only [52]

[4]intra-operative plus up to 3 days post-operative blood loss

[5]venous thrombo-embolism.

3.11. Thrombotic Disorders

In studies for marketing approval and the CUP blood biochemistry markers and clinical manifestations of hepatic dysfunction were not adversely affected during danaparoid exposure.

Therefore in Japan from the year 2000 danaparoid was investigated:

• in adults for the treatment of thrombosis in the splanchnic circulation, mainly portal vein thrombosis (PVT) and,

• mainly in children with haematogenous cancers, for the prevention of serious hepatic complications of the conditioning chemotherapy required for haematological stem-cell transplantation (HSCT), i.e. transplant associated thrombotic microangiopathy (TA-TMA) and sinusoidal obstruction syndrome (SOS).

4. Splanchnic Thromboses

4.1. Portal Vein Thrombosis Treatment

Splanchnic thromboses include complete/partial occlusion of one or more of the hepatic portal (PVT), mesenteric and splenic veins, and the hepatic vein (Budd-Chiari syndrome). PVT/splanchnic thromboses complicate hepatic cirrhosis, liver transplantation [61,62], chronic hepatitis, hepatic steatosis, recent splenectomy, paroxysmal nocturnal haematuria (PNH), chemotherapy for abdominal cancers, inflammatory disorders of the gut, thrombocytosis and COVID-19 vaccine-induced thrombotic thrombocytopenia (VITT)[63]. PVT may spontaneously resolve but complete or clinically relevant recanalisation (≥50 %) is significantly more frequent in anticoagulated patients [62]. Its persistence may lead to cavernous transformation, cause portal hypertension or adversely affect the long term outcome of hepatic cirrhosis [64-67]. PVT, either alone or with other thromboses of the group, was cited most frequently as the reason for danaparoid use.

Table 12 is based on articles [68-98] providing the exact number of patients receiving danaparoid. Of the total 1032 patients with

danaparoid all but three were in Japan. Patients' ages ranged from 23 to 85 years and 64.9% were male. Co-morbid problems were cirrhosis 93.8% (72.7% with Child-Pugh grades B and C) that mainly followed viral hepatitis, varices 77.4% and hepatocellular cancer 46.7%.

The daily dosing regimen and administration route in Japan were those approved for DIC treatment, i.e. 1250–2500 U/day as 1 or 2 i.v. bolus injections (or short infusions) since no specific dose-finding studies were performed for PVT management. Treatment for mainly 2 weeks was usually overlapped with warfarin (in a few cases a DOAC). Only the four non-Japanese cases [70-73] received the danaparoid i.v. infusion regimen since these patients had developed HIT as a result of initial use of a heparin to treat the PVT and/or HVT. In one of these patients it was used safely up to and after orthotopic liver transplant and to anticoagulate the cell saver during surgery [71].

In most patients with PVT the hepatic problem results in reduced synthesis of antithrombin (AT), thus increasing their risk of recurrent/chronic PVT. This also makes them less responsive to the heparins and may invalidate plasma anti-Xa activity monitoring because the levels do not correspond with the administered heparin dose [99, 100]. Low plasma AT levels are also associated with a worse prognosis in cirrhotic patients [101]. Hence Japanese patients with low (<60%) plasma AT levels routinely received intermittent AT injections. While danaparoid is less sensitive to low plasma AT levels than the heparins its efficacy is reduced at levels <30% [96]. Hence it is important to check for hereditary or acquired AT deficiency if danaparoid resistance is encountered, i.e. the plasma anti-Xa activity does not match the danaparoid dosing intensity. Despite claims that patients receiving both danaparoid and AT respond better than those receiving either drug alone[69, 74] this is not supported by a recent Japanese survey [102].

Table 13 presents an indirect comparison of pooled clinical outcomes of published studies including 4 or more (range 4-90) danaparoid treated patients [64, 69, 74-81, 103] with other active treatments (AT, UFH, warfarin, singly or in combination) and no treatment [102, 104-109] during the same time period.

The results show that danaparoid appears as effective as other anticoagulants but is significantly safer. PVT recurrence within the following 3 months after danaparoid discontinuation was common and could be prevented/treated by extending the danaparoid treatment period from 2 to 4 weeks and/or transitioning to an oral anticoagulant. About 25% of danaparoid treated patients also received AT supplementation, but the overall results suggest that in patients with normal plasma levels it did not significantly improve the results of danaparoid alone [102]. Two studies [82, 83] assessed vessel volume reduction as a measure of recanalisation: one with 41 patients [82] expressed the result as the mean reduction of 55.1% ± 40.2% at 2 weeks, the other with 64 patients [83] found a reduction from a median 3.43 cm3 to 1.42 cm3, also at 2 weeks. Several reports commented that chronic PVT or cavernous transformation responded least efficiently to danaparoid use. In all reports providing data the plasma levels of coagulation markers: d-dimer, TAT and fibrinogen, normalized by 2 wee ks.

Reduced platelet counts at presentation recovered in all but one patient (no reason provided) and plasma AT levels, whether above 60% before danaparoid treatment initiation or supplemented with injected AT, did not diminish during danaparoid use, emphasizing its lesser dependency than the heparins on AT levels. PVT recurrences were usually re-treated with danaparoid or the treatment period was extended to 4 weeks. Acute PVT responded more favorably to danaparoid use than chronic PVT and cavernous transformation.

Two major bleeding events were reported during danaparoid treatment: a peritoneal haemorrhage that responded to treatment [82] and esophageal ulcer bleeding following endoscopic variceal ligation after which danaparoid could be restarted [77].

Seventeen deaths were recorded during or within a year of danaparoid discontinuation. Fifteen (17%) occurred in a single study of 90 cirrhotic patients, 40 of whom had hepatic cancer. One patient developed PVT six weeks after pancreatic cancer surgery and despite combined danaparoid and thrombolytic therapy portal hypertension and a fatal ascites infection developed [85]. In the other patient splanchnic thromboses complicated HIT that developed after bowel resections for vascular insufficiency. However despite his thrombophilic state he received prophylactic danaparoid dosing and died after further bowel and liver necrosis [74].

4.1. Portal Vein Thrombosis Prophylaxis

Danaparoid also provided effective PVT prophylaxis following splenectomy in three studies [84-86] (two compared with a LMWH or warfarin). Of the 42 danaparoid treated subjects 2 (2.4%) developed a post-operative PVT compared 33%with no prophylaxis and 16.7% with warfarin.

Table 12: Off-label reports danaparoid use for Hepatic Disorders.

Off-Label use for Extra and Intra- Hepatic Thrombotic Disorders	N
Splanchnic thromboses (mainly PVT)[1]	
- treatment	955
- prophylaxis	77
Micro-circulation thrombosis prophylaxis	
- SOS, TA-TMA[2]	574
Total	1605

[1]splanchnic circulation thromboses, mainly PVT
[2]sinusoidal obstruction syndrome, transplant associated thrombotic microangiopathy.

Table 13: Pooled (indirect) PVT treatment outcomes.

Treatment	n	PVT re-canalisation[1]	PVT no change[2]	PVT progression	Major bleeding
Danaparoid ± Antithrombin	679	74.30%	17.80%	7.80%	0.30%
Other anticoagulants[2]	325	71.20%	25.40%	3.40%	7.00%
None	265	64.90%	17.00%	18.10%	3.50%

[1]from complete to 50% recanalisation

[2]from no change to 49% recanalisation

[3]AT only, (LMW)Hs and/or a VKA ± AT.

4.2. Prevention of Intra-Hepatic Thrombotic Syndromes

If serious, i.e. causing organ failure, SOS and TA-TMA after stem cell transplants have a mortality of >80%. Fortunately their frequency has been reduced to <5% with better transplant management but it remains a greater problem for children [110-112]. Danaparoid use to prevent SOS and TA-TMA has only been studied in Japan [46-48, 113-125]. Treatment outcome data is available for 518 patients [46-48, 112-125]. In two reports [46, 124], 45 of the initial 194 children received danaparoid with thrombomodulin (rTM) for a second HSCT after leukaemia recurrence. Malignancies, particularly haematogenous cancers, formed about 80% of the reasons for HSCT, while the non-malignant reasons were mainly aplastic anaemia, adrenoleukodystrophy and mucopolysaccharidoses. The subjects, mostly children (>51.8%) (age range <1-18 years), presented with a wide spectrum of clinical complications had had or were still receiving a cocktail of prophylactic medications to prevent transplant rejection and infection. Many of these medications were also risk factors for SOS or TA-TMA because of their hepato- and/or renal toxicity. Danaparoid was used alone [46, 47, 113, 115] or with ursodeoxycholic acid (UDCA) [48, 116, 117, 118-122].

Some studies compared danaparoid ± UDCA with UDCA [106] or dalteparin ± UDCA [47, 48, 117]. Dosing regimens are shown in Table 14. The reports, include three comparative studies with a total of 311 subjects exposed to danaparoid. One compared danaparoid against dalteparin [44] and two compared danaparoid plus UDCA against dalteparin plus UDCA. One of the latter studies enrolled predominantly adults (age range 16–70 years [43]) and the other [45] enrolled children aged <1 – 18 years. The remaining 234 subjects were predominantly children treated almost equally with danaparoid or danaparoid plus UDCA. In the 2 studies with data males predominated (64.2%). Danaparoid was also used with recombinant thrombomodulin (rTM) to treat 29 patients with TA-TMA/SOS [46, 114, 117, 121].

Without the advantage of specific danaparoid dose-finding studies the dosing regimens reported in adults for SOS/TA-TMA prevention (see Table 14) were based on the regimen approved for DIC treatment. Virtually all children, however, received 60 U/Kg/day (usually as 2 short infusions). Thus the daily paediatric dose is almost twice that received by Japanese adults for the same indication (approximately 30-45 U/Kg/day).

Pooled available outcomes of the studies are shown in table 15. Outcome survival (OS) and treatment-related, non-relapse mortality (T/NRM) are shown for up to a year post-transplant, but the trends shown continued to 3 and 5 years follow-up.

This indirect comparison suggests that danaparoid reduces SOS/TA-TMA frequency in patients undergoing HSCT at least as well as a LMWH and UDCA and with a lower frequency of bleeding at the dosing regimen used. More importantly it appears that 2500 U danaparoid, with or without, UDCA reduced treatment-related mortality (TRM). Unfortunately the study comparing danaparoid plus UDCA with UDCA alone and with dalteparin plus UDCA [122] did not provide an explanation for reducing the danaparoid dose to 1250 U o.d. The frequencies of SOS occurrence in this study were 15.2%, 14.4% and 13.5% respectively suggesting that 2500 U danaparoid/day provides better SOS prophylaxis. One patient treated with dalteparin but no patient on danaparoid developed HIT.

The pooled clinical outcomes suggest that the combination of danaparoid with UDCA is provides a greater efficacy/safety ratio than either product alone. Danaparoid also compare favorably with defibrotide [126-129] and the higher paediatric dosing intensity did not affect its safety.

It is interesting that no Japanese article mentions monitoring of plasma anti-Xa activity. However this did not appear to give rise to safety issues.

Table 14: Dosing Regimen information available for Danaparoid, ursodeoxycholic acid (UDCA) and Dalteparin.

SOS/TA-TMA[1] prevention with:	Adults	Children
	Dosing Regimen	Dosing regimen
Danaparoid only	2500 U/day i.v.	60 U/Kg/day i.v.
Danaparoid (+ UDCA)	1250 U/day i.v.[2]	60 U/Kg/day i.v.[3,4]
Dalteparin only	3000 IU/day i.v. infusion	No data
Dalteparin (+ UDCA)	2500-3500 IU/day i.v.[1]	70 IU/Kg/day i.v.[5]
UDCA only	600 mg/day	No data

[1]sinusoidal obstruction syndrome/transplant associated thrombotic microangiopathy

[2]plus UDCA 300-600 mg/day for adults

[3]plus UDCA 10 mg/Kg/day for children

[4]some studies used an i.v. infusion of danaparoid.

Table 15: Clinical Outcomes of Danaparoid use for SOS/TA-TMA Prevention.

Antithrombotic and/or UDCA used	%[1] Frequency of Clinically Important Treatment Outcomes					
	N	SOS	TA-TMA	T/NRM	OS	MB
Danaparoid only	258	2.3	5.4	5.4	64.1	1.93
Danaparoid + UDCA	260	9.3	0	1.7	73.3	0.5
Dalteparin only	59	22	No data	20.3	49.3	10.2
Dalteparin + UDCA	148	13.5	15.6	20.8	60.4	2
UDCA only	195	14.4	No data	8.2	72	5.1
Defibrotide	684	5.1	4	17	71	13.6

GvHD = graft v host disease, MB = major bleeding, OS = outcome survival, SOS = sinusoidal obstruction syndrome, TA-TMA = transplant associated thrombotic microangiopathy, T/NRM = non-relapse related mortality, i.e. treatment related mortality TRM, UCDA = ursodeoxycholic acid.

[1]N is the total number of patients, but not all the included articles reported al the clinical end-points shown. Hence the total number of patients contributing to these end-points is taken into consideration.

[2]total is for only acute GvHD (grade II–IV) at 3 months

[3]1 on danaparoid fatal

Table 16: APS Pregnancy outcomes during danaparoid exposure.

Source	Pooled Results of Three Comparative studies			Case reports
Treatment	Dan ± LDA	UFH ± LDA	LDA or Steroids	Danaparoid only
N total	46	94	25	35
Treatment outcomes				
No birth outcome data	0	0	0	7
N for birth outcome data	46	94	25	28
Early fetal loss ≤20weeks: abnormal karyotype	10	13	11	6
normal karyotype	6	2	3	nd
no karyotype data	1	6	8	nd
	3	5	0	6
Adjusted early fetal loss[1]	4/40 10.0%	11/92 12.0%	8/22 36.4%	6/28 21.4%
Stillbirth (loss >20 weeks)	1/46 2.2%	1/94 1.1%	0	1/28 3.6%
Medical termination	0	0	0	1/28 3.6%
Adjusted live birth rate[1]	35/40 87.5%	80/92 87.0%	14/22 63.6%	20/28 71.4%
Prematurity % live births[2]	17.20%	8.20%	14.30%	11/22 50.0%
Newly diagnosed HIT	0	1	0	0

[1]excluding pregnancies with known abnormal karyotype

[2]no data from 1 comparative study [58]

[3]Percent of patients with presenting skin rash

ALT = alanine amino transferase, AST = aspartate amino transferase, AT = antithrombin, Dan = danaparoid, LDA = low dose aspirin (80 mg), n(c)d = no (consistent) data, P-T = pre-treatment, UFH = unfractionated heparin.

5. Auto-Immune Thrombotic Syndromes

5.1. Antiphospholipid Syndromes

Danaparoid is reported to have been used in 146 patients with antiphospholipid syndromes (APS), comprising 81 non-HIT pregnancies (see Table 16) and 65 non-pregnant patients (see Table 17).

Experience of APS in pregnancy involved subjects who had suffered a median 2 miscarriages (range 2 – 9) at <20 weeks gestation or fetal growth retardation and includes three comparative studies [56-58].

It appears that in these patients with APS the live birth rate (excluding fetal deaths due to a pre-treatment chromosome aberration) with danaparoid is similar to that with heparin. Despite a higher prematurity rate this was for many women their first successful pregnancy.

The characteristics of the remaining 65 APS patients [130, 131-156] and their clinical outcomes are summarised in Table 16. The 48 acute HIT patients included 7 children aged between 10 and 17 years.

Presenting thromboses and additional clotting problems (PC, PS, AT deficiency, clotting factor antibodies, FVL) were most prevalent in acute/remote HIT patients (66.7% v 40% and 16.7% v 0% respectively). Several patients had their initial danaparoid dosing increased in response to a new TE with full recovery. Danaparoid was usually transitioned to an oral anticoagulant after a median 12 days (range 1-240 days) treatment.

Four non-fatal thrombotic events during danaparoid administration led to its discontinuation:

• bilateral PE with danaparoid cross-reactivity confirmed by SRA testing, however, is it unknown how long before UFH had been discontinued due to HIT [151].

• a DVT after successful resolution of an intracardiac thrombus that complicated HIT in a 13 year old girl[156].

• a DVT that developed on Day 1 of danaparoid exposure in a HIT patient who had received heparin for a VTE [130].

In addition, thoracic aorta dissection occurred in a patient receiving 750 U s.c. danaparoid daily to alleviate diabetic proteinuria and an aortic rupture during recovery from CABG, in a patient with undiagnosed Marfan's syndrome. Despite severe blood-loss the patient survived after repair under danaparoid anticoagulation[130].

The two deaths were caused by:

• an extensive intra-vascular leiomyosarcoma [138]

• gut necrosis due to a mesenteric infarct that occurred 1 week after danaparoid was transitioned to warfarin. The patient was awaiting hepatic transplantation [130].

A comparison of clinical outcomes of danaparoid treatment with other antithrombotics in non-pregnant subjects is currently not possible because most received danaparoid after a heparin had induced acute HIT(T) – combining two highly thrombotic disorders.

Table 17: Characteristics and Presenting Haemostatic Problems.

APS patient presenting data & clinical outcomes	Demographics & Treatment outcomes	
N	65	
Females	43	66.2%
Males	22	33.8%
Acute HIT	48	73.8%
Thromboses	42	64.6%
Clotting factor abnormality	13	20.0%
Organ failure	8	12.3%
Danaparoid dosing intensity		
Therapeutic (>2250 U/day)	45	69.2%
Prophylactic (≤2250 U/day)	11	16.9%
Unknown	9	13.8%
TE[1] during danaparoid exposure	5	6.2%
Major bleed during danaparoid exposure	2	3.1%
No problem with danaparoid or 'Recovery'[2]	55	85.9%[3]
Mortality	2	3.1%

[1]excluding TEs that were treated by increasing the danaparoid dosing intensity

[2]recovery allowing danaparoid transition to a long term oral antithrombotic

[3]no clinical outcome data for 1 subject.

5.2. COVID-19 & Vaccination-induced Thrombocytopenia and Thrombosis (VITT)

Both COVID-19 infection and some anti-COVID vaccines are associated with inflammatory and thrombotic complications. Anti-PF4 antibodies develop in most patients and their level correlates with disease severity [157, 158]. Danaparoid has anticoagulant and immune-modulation/anti-inflammatory actions, including a unique ability among approved anticoagulants to disrupt heparin-PF4-IgG and interfere with the interactions of the heparin-PF4 antibodies in patients with HIT [23-25]. It has similar activity against PF4-IgG complexes in VITT and post-vaccinated COVID-19 patients [26, 159], suggesting it could be useful in the management of both disorders [30, 31, 159].

Despite the fear of intracranial bleeding [160-162] in patients with cerebral sinus thrombosis anticoagulants are not contra-indicated [163] and danaparoid has been used safely in many cases of intracranial bleeding. Thus danaparoid use has been reported for 7 COVID-19 cases [164-167] and 19 post-vaccination VITT cases [168-180].

Table 18 summarises the main characteristics and presenting clinical status provided in the above reports. The vaccines reportedly used in subjects presenting with VITT were the AZ n=23, Pfizer n=1 and Modena n=1 (this patient had not reacted to a previous vaccination with the Pfizer product). The time to hospital admission after vaccination was a median 10.5 days (range 7 – 59 days).

No patient had a prior thrombophilic marker but all of 17 tested showed an increased plasma D-dimer level and 3 of the 4 tested had low fibrinogen levels. For only 2 cases was danaparoid the first choice treatment otherwise for 1 COVID-19 and 8 VITT cases it was the second choice hence its initiation was delayed. There is no information for the remaining cases.

Danaparoid dosing schedules were provided for only 2 patients with COVID-19 and 14 with VITT:

• for TE complicating COVID-19 both received 1250 U b.d., s.c. for 15 days in one subject and 5 days in the other, after which it was reduced to 1250 U mane and 750 U nocte for another 14 days.

• the danaparoid dosing for VITT was provided as a therapeutic i.v. infusion (Regimen 2 up 8000 U/day) in 4 patients. Of the remaining 10 patients 2 received prophylactic dosing of 750 U b.d., s.c. and 8 patients received therapeutic dosing levels of 2250-5000 U as 3-4 injections/day.

• steady-state plasma anti-Xa activity in the 5 patients with information was 0.23 – 0.5 U/mL.

• eleven VITT patients also received IgG injections.

Table 19 summarises the known clinical outcomes during and after danaparoid exposure. The 2 new TEs in the VITT group were an extension of the presenting cerebral venous sinus thrombosis on Day 4[168], and the development of a superficial arm DVT and a PVT[179]. Both patients were initially underdosed with 750 U s.c., b.d., danaparoid, but for the latter patient danaparoid was increased after 2 days to 1500 U s.c., b.d. for 2 days and finally 1250 U for 13 days during which time both thromboses resolved.

During hospitalization intracranial bleeding caused or contributed to death in 2 patients:

• two days after discharge following hospitalization for a DVT, that occurred 10 days after Ad26.COV2.S vaccination, one patient suffered a cerebral sinus thrombosis with bleeding whilst on therapeutic Tinzaparin. Despite i.v. IgG and therapeutic danaparoid treatment the patient died [175].

• the other patient (BMI 40) presented with intracerebral bleeding. Danaparoid treatment was initiated but because his plasma anti-Xa activity response (0.23 U/mL) was insufficient the maintenance danaparoid infusion rate was increased to 250-330 U/h. The bleeding fatally increased [179].

In another patient therapeutic danaparoid was switched to fondaparinux and steroids for discharge after his PCR, D-dimer and clinical signs improved. However 55 days later a fatal ICH occurred.

5.3. Diabetic Nephropathy and Retinopathy

Diabetic nephropathy affects 30-40% of insulin-dependent diabetics. It's development was considered to be related to the loss of heparan sulphate from the glomerular basement membrane by the increased activity of heparanases in renal disorders. This reduces the negative charge that controls the sieving of proteins by the glomerular basement membrane (GBM) resulting in proteinuria, renal failure requiring ECC support and eventually the need for renal transplantation. It was therefore conjectured that danaparoid with its high content of heparan sulphate could alleviate the proteinuria of diabetics. Indeed a study [181] showed danaparoid was equivalent to enalapril in reducing proteinuria in streptozotocin treated diabetic rats.

In a small blind cross-over pilot study [182] 9 stable insulin dependent diabetics, aged 14 to 31 years, were randomized to either 6 weeks danaparoid 750 U daily or 6 weeks placebo followed by a washout period of 4 weeks. Then the treatment (danaparoid or placebo) for each subject was reversed for the following 6 weeks. The results showed a significant decline in both albuminuria and proteinuria ($p=0.001$) during the danaparoid treatment periods compared with the placebo treatment periods. The AER/creatinine, the protein excretion rate standardized for creatinine excretion and the mean percentage change in urinary protein/creatinine ratio all significantly improved during danaparoid treatment ($p=0.03$, 0.05 and 0.001 respectively). There were no haematological or plasma enzyme changes. In addition, examination of fundus photographs [183] showed that before the study 14 of the 18 eyes had grade 1-4 hard exudates and 4 eyes had no exudates. Repeat photographs after study completion showed improvement in 10 and no progression in 4 of the 14 eyes with hard exudates but only after the danaparoid treatment episodes and no deterioration in the other 4 eyes.

However, it is unclear whether danaparoid is indeed replacing heparan sulphate in the GBM and/or inhibiting heparanase activity since the low surface charge density of danaparoid is unlikely to restore the sieving functionality of the endogenous renal HS. There is also evidence that loss of HS, (largely in the form of proteoglycan adhesion molecules important for podocyte attachment) from the GBM does not (directly) induce proteinuria [184-187. However, similar study [188] in non-insulin dependent diabetics did not show improvement in either nephropathy or retinopathy. These results suggest that Type 1 diabetes has a different pathogenesis from Type 2 and that the effect of danaparoid is not simply explained by danaparoid restoring heparan sulphate.

Table 18: Presenting data of COVID-19 and VITT patients.

Patient data at presentation	COVID-19	VITT
N	7	19
Gender male/female	7/0	07-Dec
Age (mean y):		
male	60	45
female	-	45
Platelet counts: mean on admission/nadir	201/59	70/54[1]
Pre-danaparoid TE:		
arterial	2	4
venous	2	152
4T score	5	no data
Pre-danaparoid major bleeding	0	63
On ventilation/ECMO	4	0
Positive tests for anti-platelet antibodies[5]		
anti-PF4	04-Apr	04-Apr
SRA	Jan-15	0/1
HIPA	04-Apr	01-Apr
E(L)I(S)A	Jan-15	09-Nov
IgG specific	Jan-15	7
Any test positive	5	17
Not tested	2	2

[1]of the 11 patients with data had normal counts on admission but then developed a >30% reduction

[2]intracerebral vein thrombosis in 10 subjects, both arterial and venous thrombosis in 2 subjects

[3]five intracranial and 1 at multiple sites

[4]first number = positive test, second number = total number tested

[5]one patient screened with all 3 tests.

Table 19: Events during Danaparoid Treatment in COVID-19 and VITT Patients.

Outcome	COVID-19	VITT
n	7	19
New thromboembolic event	0	2
New major bleeding event	0	1
Persistent thrombocytopenia	0	31
Deaths	0	22

[1]in 1 patient platelets recovered after IgG injections. One patient recovered after switching to argatroban and then to dabigatran, the 3rd patient after switching to fondaparinux.

[2]both due to intra-cranial bleeding (in one patient present prior to danaparoid treatment initiation).

6. Discussion

After almost 50 years danaparoid is hardly used for its originally approved indication for VTE prevention. Similarly, it is now mainly confined to HIT management in pregnancy or renal failure or HIT unresponsive to other treatments despite continuing [189-191] recommendations for its use[This is mistakenly because of fears of cross-reactivity with the HIT antibody, bleeding risk and supply problems.

Nevertheless danaparoid has several advantages over the heparins:

1. the HA-HS chains that could cross-react with the HIT antibody and either cause or exacerbate its clinical effects are overwhelmingly prevented from doing so by the NA-HS chains of danaparoid,

2. it is almost 100% bioavailable because it is not inactivated by heparin-binding proteins,

3. there is no tendency for rebound thrombosis after treatment discontinuation,

4. it is less dependent on the level of free AT in the circulation,

5. it is at least as safe. and also possesses some important advantages over many current antithrombotics:

1. it combines anti-inflammatory and immune modulation activities,

2. it shows a unique ability to suppress the immune interactions that produce and amplify clinical manifestations associated with PF-4 antibodies.

Hence for the above reasons danaparoid has been increasingly investigated in off-label disorders, particularly extra and intra hepatic thrombotic syndromes, APS, COVID-19 infection and VITT. The results are encouraging despite some of these disorders being contraindications and warnings in the package insert, e.g. use in patients with a positive pre-treatment cross-reactivity test, severe bleeding risk, hepatic dysfunction and intra-cerebral bleeding or spinal damage. However, excluding intra-hepatic thrombotic syndromes in children, there is still a clear need for proper dose setting/safety studies.

The efficacy of 2 weeks danaparoid intermittent injections for splanchnic thrombosis treatment compares favorably with other anticoagulants including dabigatran followed by warfarin for 30 months [19]). Hence it has become one of the main anticoagulants, with or without AT, for PVT treatment in Japan [102, 103, 192]. However, PVT recurrence is a frequent challenge and it has been observed that danaparoid treatment extension from 1 or 2 weeks to 4 weeks [62, 84, 86, 88] and/or a higher dosing intensity (unspecified) were more effective[84]. Indeed the 3 non-Japanese patients with HIT and multiple splanchnic thromboses [71-73] had no safety or efficacy problem with therapeutic danaparoid infusions. Despite the lack of a dose finding study we advise, in line with routine thrombosis treatment [4], that the intermittent injection Japanese dosing regimen is replaced with at least a week of therapeutic i.v. danaparoid administered as a continuous infusion. This can be followed by either prophylactic danaparoid dosing if the PVT has not completely re-canalised and/or transitioned to oral anticoagulation for 3-6 months to reduce the frequency of PVT recurrence. The continuous danaparoid infusion maintains the correct levels and ratios of its inter-active constituents in the plasma at all times thus eliminating the peaks and troughs of its plasma activities that make the intermittent i.v. dosing schedule less effective. The maintenance danaparoid infusion rate should be adjusted to achieve plasma anti-Xa activity between 0.4 and 0.8 U/mL, but to date we have not identified any Japanese clinical study that provided monitoring data. It is only necessary to monitor danaparoid once or twice during maintenance infusions to check for over or underdosing.

The combination in danaparoid of antithrombotic and immune-modulating activity may also be useful in the management of auto-immune thrombophilic disorders, e.g. APS, COVID-19 and VITT [30, 31]. There is a continuing concern for danaparoid-induced HIT or cross-reactivity with the heparin-induced anti-platelet antibodies. In-vitro studies with therapeutic levels of danaparoid have shown that unlike the heparins it is incapable of forming the ultra-large complexes with PF-4 required for antibody induction [193]. However it is uniquely capable of disrupting PF4-antibody complexes and interferes with their interaction with both heparin and platelets [23-26, 193]. Furthermore, pre-treatment test positive cross-reactivity of danaparoid with heparin-induced antibodies is most likely the result of residual heparin in patients' blood samples [194-196]. Repeat cross-reactivity testing within 48 hours of the first test were negative in all patients so investigated in the danaparoid CUP [197] and pre-treatment danaparoid cross-reactivity has not been shown to be clinically important[198-200]. Adverse clinical outcomes with danaparoid are most likely due to underdosing and delayed treatment initiation [201], co-morbidity and concomitant heparin administration. Indirect comparison [202] of therapeutic danaparoid with argatroban and hirudin, neither of which can cross-react with the HIT antibody, has shown a lower frequency of inefficacy outcomes (a composite of thrombotic events including amputation and all-cause mortality) and equally frequent platelet count recovery with danaparoid. Thus these events more likely reflect progression of the underlying pro-thrombotic disorder than danaparoid cross-reactivity. Thus danaparoid has been successfully used in a small number of COVID-19 and VITT patients leading to its inclusion in recommendations for their treatment [203, 204].

Danaparoid has been safely used in patients with intracranial bleeding and/or thrombosis including some treated with higher than recommended danaparoid dosing intensities, e.g. a 142 Kg HIT patient undergoing haemodialysis [205], an infant with intracerebral thrombosis [36] a patient with an intracardiac thrombus due to paroxysmal nocturnal haemoglobinuria [106] and in several pregnancies [206, 207]. Nevertheless, an obese, hypertensive, diabetic VITT patient with intracranial thrombosis and haemorrhage [198] developed fatal bleeding extension when his maintenance danaparoid infusion rate was increased to 330 U/h

to reach the target plasma anti-Xa activity range. It 2is important to note that for danaparoid the plasma anti-Xa activity correlates poorly with the occurrence of thrombosis or bleeding because it does not fully describe its effects on the clotting cascade. Hence, clinical judgement, especially bleeding risk, should determine the optimal danaparoid dosing intensity for an individual patient [4, 208] and unless absolutely necessary the recommended infusion rates[4] should not be exceeded.

7. Conclusions

Pooled reported clinical outcomes suggest that danaparoid use is safe and efficacious for off-label 'contra'-indications such as: thrombotic problems in non-HIT pregnancies and children, hepatic failure and patients presenting with bleeding complications. However for some clinical situations it is advised that because of its multifaceted pharmacokinetics danaparoid should be administered as a continuous infusion instead of intermittent i.v. or s.c. injections. This takes full advantage of its antithrombotic and immune-modulatory actions, but should be validated by dose-finding studies.

In many off-label disorders danaparoid appears to provide a safe, effective therapeutic effect and there is sufficient comparative data in a reasonable number of patients to show its superiority over some standard therapies.

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