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Review Article

Danaparoid Sodium (Orgaran®): An Update on its Approved Indications

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Abstract

Background: This review updates the rationale for danaparoid use and the clinical outcomes reported for its approved indications, while identifying areas in which its use may be optimized. Danaparoid, a low-molecular-weight heparinoid, is approved for deep-vein thrombosis prophylaxis and for the treatment of heparin-induced thrombocytopenia (HIT) and disseminated intravascular coagulation (DIC). It consists predominantly of heparan sulphate, of which a small fraction mediates anti-Xa activity through Antithrombin binding, whereas the larger fraction contributes importantly to thrombin generation inhibition and appears to modulate the actions of anti-PF4/polyanion antibodies and attenuate inflammatory responses. These features distinguish danaparoid from other approved antithrombotic agents.

Methods: From an extensive literature search covering 1981 to 2026, new publications, particularly from Japan, have been identified that extend our knowledge of danaparoid.

Results: Despite established dosing recommendations and a substantial body of efficacy and safety data, the clinical value of danaparoid may be underestimated because its pharmacologic behaviour is often misunderstood. This can lead to inappropriate dosing choices. In addition, contraindications and warnings may discourage danaparoid use in clinical settings in which it has shown value. In Japan, the intermittent dosing regimen approved there for DIC has been used unmodified for routine prophylaxis and thrombosis treatment with mixed results. Because of the complex pharmacokinetics of danaparoid, this regimen may be inappropriate in situations where continuous thrombotic and anti-inflammatory protection is required and also for routine thrombosis prophylaxis.

Conclusion: Adopting the established separate dosing recommendations for thrombosis treatment and prophylaxis could improve clinical outcomes. In particular, the therapeutic regime of an intravenous loading bolus followed by continuous therapeutic infusion may better sustain the interactions between danaparoid's active components and thereby optimise its anticoagulant and immune-modulatory effects.

More Information

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Keywords: Danaparoid; (Under) dosing; Antithrombotic; Anti-inflammatory/immune modulation; Heparin-induced thrombocytopenia; Disseminated intravascular coagulation

Introduction

Danaparoid is a natural mixture of glycosaminoglycans (GAGs) isolated from porcine intestinal mucosa. The purified product is a white to faint-yellow powder that is free of heparin. It consists of short-chain linear GAGs with an average molecular weight of 4,500 Da (range 2,500–10,000 Da) [1] and is composed of approximately 85% heparan sulphate (HS), 12% dermatan sulphate (DS), and a small proportion of inactive chondroitin sulphates. The HS fraction can be subdivided into approximately 95% with no affinity for Antithrombin (NA-HS) and 5% with high affinity for Antithrombin (HA-HS).

Unlike the heparins, the NA-HS chains consist largely of glucuronic acid [2] disaccharides with a relatively low degree of sulphation and negative charge density. By contrast, HA-HS chains carry a higher negative charge because each contains the highly sulphated pentasaccharide sequence required for Antithrombin (AT) binding. Intact danaparoid shows little binding to circulating cationic heparin-binding proteins apart

from its intended targets within the coagulation cascade. This contributes to its almost complete bioavailability, compared with approximately 30% for unfractionated heparin and up to 80% for low-molecular-weight heparins. Anti-Xa activity units for danaparoid are therefore not interchangeable with heparin international units, and plasma anti-Xa assays must be calibrated specifically for danaparoid to avoid overestimation, dosing error, and potential bleeding.

Pharmacology

Pharmacodynamics

Antithrombotic activity: Danaparoid inhibits fibrin formation primarily through thrombin generation inhibition (TGI), which reflects the combined actions of the HA-HS and NA-HS subfractions [2,3]. As shown in Table 1, these subfractions appear to contribute approximately equally to its antithrombotic effect [2]. Unlike heparin, HA-HS binding to antithrombin is reversible [4], which may allow Antithrombin (AT) to retain additional anti-inflammatory functions, particularly at the vascular endothelium [5]. HA-HS and DS also provide smaller indirect antithrombin effects through AT and heparin cofactor II, respectively [2]. In animal models, danaparoid has shown a more favourable balance between antithrombotic efficacy and bleeding than unfractionated heparin and first-generation low-molecular-weight heparins [6].

Even at therapeutic intensity, danaparoid has little effect on routine clotting tests such as the activated partial thromboplastin time, prothrombin time, thrombin time, and activated clotting time [2]. Historically, monitoring was therefore based on its linear dose–response relationship in amidolytic anti-Xa activity assays [6]. Importantly, the elimination half-life of plasma anti-Xa activity (24.5 h) reflects only the minor HA-HS component, which accounts for roughly 4% of the total mass and does not represent the overall activity of intact danaparoid.

Danaparoid has minimal effects on platelet function [2], so clots formed during treatment remain relatively platelet-rich and primary haemostasis is largely preserved. It also suppresses thrombin-induced generation of procoagulant platelets through an AT-independent mechanism [8]. After intravenous administration, danaparoid neither binds to platelet factor 4 nor induces its release [9,10]. It does not cross the guinea pig or human placenta [11,12] and is not excreted into breast milk in amounts likely to be clinically relevant [12,13].

Fibrinolytic activity

At therapeutic doses, danaparoid does not appear to have a direct effect on fibrinolysis. For example, it does not shorten euglobulin clot lysis time, alter plasma tissue plasminogen activator or α2-antiplasmin levels, or induce release of fibrin degradation products such as fragments E and Bβ15-42 [14]. It may, however, facilitate fibrinolysis in vivo by increasing clot permeability to plasmin [15,16].

Anti-inflammatory/Immune modulatory actions

Danaparoid has attenuated inflammatory responses in several animal models and in a pilot human study [17-21]. It has also been shown to interfere with the immune pathogenesis of HIT [22-24] by disrupting interactions between HIT antibodies, heparin, and their cellular or platelet targets. These effects occur at therapeutic dosing levels and appear to involve both AT-dependent and AT-independent pathways. They may be relevant not only to HIT but also to DIC, particularly when associated with sepsis [25-27], and potentially to other thrombo-inflammatory disorders such as COVID-19-associated coagulopathy [28,29].

Pharmacokinetics

Table 1 summarises the elimination half-lives of the principal functional components of danaparoid. Clearance is predominantly renal, as hepatic bypass models did not show reduced elimination [8,30].

Based on animal studies, it is assumed that the half-life of thrombin generation inhibition (6.7 h), which integrates the total effects of danaparoid on the clotting cascade, correlates more closely with the functional antithrombotic half-life of danaparoid [2] than the half-life of plasma anti-Xa activity alone. Support for this interpretation in clinical practice comes from early dose-finding studies showing that twice-daily administration of danaparoid was more effective than once-daily dosing for deep vein thrombosis (DVT) prophylaxis [31,32].

Table 1: Functional aspects of danaparoid constituents.

Functional component	Mass percent of danaparoid	Clotting Cascade Action	Effect	Half-life of the Effect	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[1]	Approximately 50%
NA-HS	~80%	Direct inhibition of thrombin-activated FIXa generation			Approximately 50%
		Attenuates release of systemic inflammatory markers, Interferes with antibody interactions	Immune-modulatory Anti-inflammatory	3.5 hours[2]	Possibly indirect
CS	~4%	None	None		None

[1] The half-life of the anti-Xa activity is 24.5 hours.
[2] The half-life of the NA-HS per se, but that of its effects on the immune system, is unknown.

Since recent clinical outcome data are also available from Japanese studies, the pharmacokinetics of danaparoid in this population [33,34], represented by the plasma anti-Xa activity, has been compared with that of non-Japanese subjects [30,35] to evaluate the possibility of a racial influence. The comparison reveals similar elimination half-lives in healthy subjects and the same degree of prolongation (50-100%) in renal failure patients: 21.4 h v 24.5 h and 27.6 h and 30.8 h, respectively. Thus, in addition to the lack of influence of age and gender, racial difference also does not affect danaparoid elimination.

Although the elimination half-life of anti-Xa activity is prolonged in patients with renal failure and plasma anti-Xa activity tends to remain stable during haemodialysis, it declines during the interdialytic period almost to baseline. This finding suggests that at least the HA-HS component may be metabolised by endogenous circulating heparinase [36] and/or heparanase [37], both of which reduce antithrombotic activity in vitro. Whether the same applies to the other components of danaparoid remains unknown.

Antidote

Danaparoid has no clinically validated antidote. Experimental and clinical experience in settings associated with high bleeding risk supports a generally favourable safety profile [2], and overdose does not invariably lead to bleeding. For example, a 12-month-old child with moyamoya disease [38] received danaparoid at 350 U/kg/day for 10 days and again for 15 days on separate occasions—approximately five times the adult daily therapeutic dose—without apparent complication. Nevertheless, life-threatening bleeding has been reported [39-42], even at plasma anti-Xa activities within the recommended ranges, possibly because danaparoid can facilitate thrombolysis [15,16].

In some patients undergoing cardiopulmonary bypass with danaparoid, surgical bleeding was controlled with topical fibrin sealant [43,44] or aprotinin [45], but routine reversal agents used for the heparins, including protamine sulphate, desmopressin, and ε-aminocaproic acid, are ineffective [42]. Additional supportive approaches have included transfusion of blood products, which may dilute circulating danaparoid and promote renal clearance. Plasmapheresis after cardiopulmonary bypass [46] and high-cut-off membrane dialysis in an overdosed patient [47] both reduced plasma anti-Xa activity and were associated with bleeding control within 3–6 hours. In vitro studies suggest that recombinant factor VIIa may reverse thrombin generation inhibition more effectively than FEIBA [48], and an intravenous dose of 90 µg/kg has been proposed [49]. Recombinant factor VIII has also been suggested as a potential option [16].

Pharmacy and compatibility

In most countries, danaparoid is available as Orgaran® in 0.6 mL glass break-neck ampoules containing the sodium salt dissolved in saline at pH 7. Each ampoule contains 750 anti-factor Xa units (750 U) and sodium bisulphite as preservative. Orgaran® is intended for intermittent subcutaneous or intravenous injection, or for continuous intravenous infusion, but it must not be administered intramuscularly.

For continuous infusion, the stock solution may be prepared by adding three ampoules of 750 U/0.6 mL (total 2250 U) to 250 mL of 5% glucose. This produces a solution containing 9 U/mL, which can then be infused at the rates shown in Table 2 to achieve the desired hourly dose.

Table 2: Danaparoid stock solution of 9 U/mL infusion rates.

Desired danaparoid rate (U/h)	Stock infusion rate (mL/h)	Actual danaparoid rate (U/h)
100	11	99
150	17	153
300	33	297
400	44	396
600	66	594

Monitoring

Plasma anti-Xa monitoring is not required during routine venous thromboembolism prophylaxis, but it may be helpful to:

- avoid accumulation in paediatric patients, smaller adults, and patients with severe renal impairment;
- ensure that patients with obesity are not underdosed [50];
- guide dose adjustments, particularly when the patient's clinical condition deteriorates.

Dosing regimens

Detailed dosing recommendations covering a wide range of clinical situations [51] are available. However, in Japan, 1250 U once or twice daily intravenously, approved for DIC treatment, is also used routinely in adults for thrombosis prophylaxis or treatment in medical and surgical scenarios [52-57].

Methods

The authors have used Internet search engines, e.g., Google Scholar, PubMed, and NCBI, to identify books, theses, articles, abstracts, and letters with clinical outcome data of patients exposed to danaparoid from January 1981 to May 2026. Care has been taken to recognize and eliminate duplicate publications of the same patient(s) by the same or different authors. The database for the DIC post-marketing surveillance study (PMS) in Japan 2003-2006 is not publicly available, but the corresponding author was granted a copy that can be shared.

p - values were calculated using Fisher's exact test.

Approved Indications

Clinical development: Clinical development of danaparoid

began in 1981, and between 1991 and 1997 it was approved in many countries for routine DVT prophylaxis in patients undergoing orthopaedic surgery or major cancer surgery and in some countries for thromboprophylaxis in patients with ischaemic stroke. Approval for the treatment and/or prevention of HIT followed in 1994, and in Japan only for the treatment of DIC in 2000. Initial studies were only performed in Caucasian subjects, but more recently interesting data from Japan have also become available. A confounding factor with the approved danaparoid indications was that HIT and DIC often complicated treatment in patients with major medical and surgical problems. Many of these problems were listed as contraindications or warnings for danaparoid use in the original approval for DVT prophylaxis. As a result, they are still cited as reasons to avoid danaparoid treatment or to reduce its intensity. Since the danaparoid approvals, many studies supporting the safety and efficacy of danaparoid use have become available.

Aims of this review

Our aim in this review is to provide evidence that in many clinical situations danaparoid avoidance or treatment intensity reduction is unwarranted. We also wish to emphasize the importance of following the published [51] dosing recommended for each clinical situation.

Contraindications, warnings and precautions: Contraindications, warnings, and precautions agreed during regulatory discussions preceding marketing approval were largely based on limited early data and analogy with other antithrombotic agents.

Danaparoid is contraindicated in patients with:

- 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
- hypersensitivity to the active substance or to any of the excipients.
- a need for locoregional anesthesia, particularly if therapeutic dosing is required,
- damage to the central nervous system or brain, spinal or ophthalmological surgery.

Warnings and precautions

- danaparoid is not intended for intramuscular administration; therefore, it should not be given by the intramuscular route,
- 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 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.

At the time of approval some evidence against these restrictions was available from a large named patient compassionate use programme (CUP) and publications, but it was considered insufficient. Since then, none of the license holders for danaparoid marketing has revised these warnings and precautions in the light of increasing support for danaparoid use.

Recent haemorrhagic stroke/intracranial haemorrhage: Danaparoid was developed because of its low molecular weight. This followed studies showing that heparin activated platelets and prevented the primary haemostasis that led to bleeding complications. By reducing the length of the heparin chains, a component was found that retained anticoagulant activity and preserved primary haemostasis. Danaparoid in animal studies of bleeding was shown to be safer than both unfractionated and, in research, low molecular weight heparins. In one study to demonstrate its safety, five non-HIT patients with a haemorrhagic stroke complicated by the development of an acute DVT (one, seven, 14, and 21 days later) and in one case a myocardial infarction-induced intracardiac thrombus, received therapeutic danaparoid treatment [58]. Intravenous infusion rates of

120–240 U/h were maintained for 15–43 days, with steady-state plasma anti-Xa activities between 0.45 and 1.09 U/mL. Venography showed stabilisation of the DVT in three patients and regression in one, and echocardiography showed disappearance of the intracardiac thrombus in the fifth patient. Post-treatment brain imaging showed neither expansion of the original haemorrhage nor new intracranial bleeding. Danaparoid was also used without extension of intracranial bleeding in a 10-year-old boy undergoing haemodialysis [59] and in patients with VITT [60].

Severe bleeding diathesis or haemorrhagic risk: Bleeding or a high risk of bleeding are frequently encountered in DIC and other critically ill patients. Table 3 summarises the main clinical outcomes from 11 studies of therapeutic danaparoid use in intensive care patients [39,40,61-72]. As indirect comparisons, it also includes pooled data from studies of two direct thrombin inhibitors in similar populations [73-80]. It should be noted that collection of argatroban outcome data generally stopped when infusion ceased, usually after about two weeks, or when death occurred, whereas danaparoid and bivalirudin data include events occurring up to six and four weeks after treatment discontinuation, respectively.

Differences in the pooled frequencies of major clinical end points—thromboembolic events, major bleeding, and all-cause mortality—between danaparoid, argatroban, and bivalirudin reached statistical significance overall for thromboembolic events ($p = 0.0317$), but not for all other comparisons. Within the limits of indirect comparison, danaparoid compares favourably with both alternatives, especially about bleeding risk. These studies also support the observation that adverse outcomes are more frequent when renal failure and HIT coexist than when either condition occurs alone [81-84].

Further studies of therapeutic danaparoid in medical and post-operative ICU patients [61,62], as well as those in acute renal failure [63], acute promyelocytic leukaemia [64], and patients with varices related to portal hypertension [65-68], support the view that danaparoid generally carries a relatively low risk of bleeding.

Spinal or epidural anesthesia, lumbar puncture: Due to experience with unfractionated and low-molecular-weight heparins, the US Orgaran prescribing information from 1997 onward includes a boxed warning for neuraxial bleeding associated with anticoagulation during spinal or epidural analgesia or anaesthesia. The risk is greatest in patients requiring prolonged epidural or spinal catheterisation, those receiving nonsteroidal anti-inflammatory drugs, or those undergoing traumatic or repeated puncture. Additional caution was warranted in patients with creatinine clearance between 15 and 30 mL/min because danaparoid elimination is prolonged in this setting.

During early dose-finding and major studies [85-88] for danaparoid marketing approval, 329 of the 854 (40%) patients for peri-operative thromboprophylaxis received loco-regional (mainly epidural) anaesthesia. In all studies, the first subcutaneous 750 U dose of danaparoid was administered pre-operatively just before or just after the puncture. Two elective hip patients from one centre developed transient foot-drop after a psoas block due to small haematomas; otherwise, no problems were reported. In addition, six women after prolonged danaparoid use during pregnancy received epidural anaesthesia for caesarean section without incident. The epidural catheter was inserted in three women 24 h and in one woman 4 h after stopping danaparoid pre-operatively. In these four cases, danaparoid was restarted post-operatively, but only in two is the timing provided – six hours and two hours after delivery [12]. There is no information on dose timing for the other two women.

Thus, if current guidance for insertion and removal of epidural or spinal catheters is followed, danaparoid appears to be usable. Decisions about anticoagulation in the setting of neuraxial anaesthesia should take into account the interval since the last danaparoid dose, the patient's overall bleeding risk, and the product information. Patients should be monitored closely for neurological symptoms, and they and their nurses should be instructed to report back pain, lower-limb numbness or weakness, or bowel or bladder dysfunction immediately, because spinal or epidural haematoma requires urgent evaluation and, when indicated, decompression.

Spinal cord injury: Damage to the central nervous system may be complicated by up to 25% VTE. This was addressed

Table 3: Indirect comparison of Pooled danaparoid *vs.* Pooled DTI treatment: in Critically Ill Patients.

First author of publication	N	Clinical status						
		Pre-treatment		Post-treatment				
		HIT	Renal failure	All TEs	All MBs	All-cause mortality	PC stable or recovered	
Pooled danaparoid	356	86.5%	68.8%	7.6%	8.1%	26.7%	84.9%[1]	
Pooled Argatroban[2]	244	20.9%	none	14.3%	11.7%	23.4%[3]	[4]	
Pooled bivalirudin[5]	145	<50%	none	7.6%	15.0%	22.1%	89.6%	

[1] The denominator is 319 in the absence of data from Sturtevant et al.[70]
[2] references 73-78
[3] Only 5 studies reported mortality rates, i.e., 46 in 206 patients.
[4] data only available for 1 study to Day 3 – 58% recovery
[5] references 78-80
MBs = major bleeds, PC = platelet count, TE = thrombo-embolic events.

in a study of 67 non-HIT patients with an acute spinal cord injury [89]. The fifty-seven patients who completed this study received subcutaneous danaparoid in combination with two types of calf stimulation (see Table 4) as DVT prophylaxis for two weeks. The patients had C2 through T12 motor complete or motor non-functional injury.

Danaparoid effectively prevented DVT, particularly in the group given twice daily injections (Chi-square *p* value = 0.0180), and no bleeding or any other adverse rNo bleeding or any other adverse reaction occurred.

Renal Injury requiring extracorporeal circuit support: Patients in renal failure, particularly those with chronic injury who have anaemia due to reduced erythropoietin production, are at risk of bleeding if anticoagulants are used to prevent clotting in their extracorporeal renal replacement circuits. The prolonged renal elimination of anti-Xa activity [8, 30] and concern about accumulation in renal failure are frequently quoted as reasons for avoiding danaparoid. Nevertheless, it is potentially well suited to these patients since it does not activate platelets, has a relatively low bleeding potential, and, unlike heparin, because it does not deplete vascular endothelial lipoprotein lipase stores, it may reduce the risk of nephrogenic hypertriglyceridaemia and its cardiovascular consequences [8,90,91]. Thus, with specifically designed dosing schedules [41,51,72] to mitigate accumulation, it has been used successfully for both intermittent haemodialysis (HD) [41] and continuous veno-venous renal replacement therapy (CVVRT) [72].

Intermittent haemodialysis

Danaparoid anticoagulation for HD was first reported in 1983 in non-HIT patients with postoperative acute kidney injury and high bleeding risk [79] and subsequently dose-setting studies in non-HIT patients with stable chronic kidney disease [35,92,93] were performed. In total, 123 mainly chronic injury patients undergoing haemodialysis with danaparoid anticoagulation [9,34,39,41,50,59,63,91-102, Lassila R personal communication, 2024] have been described. While most patients received the standard dose regimen, some were treated with a continuous intravenous regimen to manage an ongoing systemic thrombotic risk during the interdialytic period. Clinical presentation and outcomes are summarised in Table 5. Plasma anti-Xa activity assay is advised for dose-setting but was often not performed or reported. Available intra/end-dialysis levels were a median 0.5 U/mL (range 0.3-0.9 U/mL), and these reduced to <0.3 U/mL within 48 – 72 hours.

Continuous renal replacement therapy

Danaparoid anticoagulation has been reported in 136 patients requiring continuous veno-venous replacement therapy [34,39,40,72,103]. Most received the recommended therapeutic continuous infusion regimen [51], often modified when circuit clotting occurred. In patients with acute HIT in particular, the initial infusion rate sometimes needed to be increased, up to 600 U/h for four hours, or the maintenance rate increased to as much as 400 U/h, to prevent fibrin deposition and restore circuit pressure and flow. The practical

Table 4: Outcomes of danaparoid thromboprophylaxis in Spinal Cord Injury.

Orgaran s.c. dose	Frequency	Calf stimulation	n	Completed	Total DVT	% DVT
750 U.	o.d.	EPC	19	16	5	18%
1250 U	o.d.	EPC	30	26	2	7%
750 U	b.d.	ES	18	15	0	0%

EPC = External Pneumatic Compression, ES = Electrical Calf Stimulation

Table 5: Danaparoid exposure in Renal Failure patients requiring ECC support.

Renal Replacement method		Intermittent Haemodialysis		Continuous Veno-Venous	
N patients		33	97	30	106
Presenting Status	HIT confirmed	All Non-HIT	66.7%	All non-HIT	84.9%
	HIT suspected[1]		33.3%		15.1%
	% AKD	36.4%	55.7%	100%	95.3%
	DIC/sepsis	34.3%	23.7%	80.0%	58.5%
	Circuit clotting	9.0%	12.4%	6.7%	21.9%
	Systemic clotting	18.2%	25.8%	10.0%	28.3%
	Bleeding risk[2]	60.1%	46.4%	13.3%	66.0%
	Other organ failure[3]	6.1%	10.3%	16.7%	43.1%
Clinical outcomes[4]	ECC patency restored	100%	93.8%	100.0%	94.7%
	Major bleeding	3.0%	5.2%	3.3%	12.3%
	Systemic TE/Circuit clots[5]	3.0%	16.5%	0.0%	6.4%
	Non-MB/TE deaths[6]	9.1%	14.4%	13.3%	36.8%
	Total 28-day mortality	9.1%	20.6%	16.7%	40.6%

[1] tests negative or not done
[2] due to recent surgery or overt bleeding
[3] respiratory, cardiac, hepatic or multiple organ failure
[4] to 3 months after danaparoid discontinuation
[5] excluding early circuit clotting during danaparoid dose optimization
[6] 28 days after danaparoid discontinuation (due to sepsis and organ failure)©©©

aim is to identify the lowest infusion rate that maintains circuit patency and acceptable filter life [37,40,103], while also providing sufficient anticoagulation when systemic thrombosis treatment or prevention is required.

Clinical characteristics at presentation and treatment outcomes, summarised in Table 5, also show trends that HIT and renal failure co-morbidity result in worse clinical outcomes, with most deaths due to sepsis and/or multiple organ failure, but only 28-day mortality reaches statistical significance (P = 0.0174). Despite this, ECC patency was restored in almost all patients, and there was no systematic evidence of danaparoid cross-reactivity.

These data for both HD and CVVRT support the safety and efficacy of danaparoid and reinforce the observation that renal failure patients with PF4/heparin antibodies have greater baseline morbidity and worse outcomes than those without these antibodies [81-84]. Continuous arteriovenous renal replacement therapy is, however, not recommended [104] because frequent bleeding at the arterial puncture site occurred that was difficult to control in the absence of an antidote.

Hepatic dysfunction

Although danaparoid is not eliminated or metabolised by the liver, hepatic dysfunction is often quoted as a reason for avoiding danaparoid use. A safety evaluation of plasma enzymes and bilirubin levels of patients in the CUP was conducted. Furthermore, its use in over 1500 Japanese adults and children with hepatic pathology (hepatic cirrhosis, varices, hepatic cancer and hepatic toxicity related to chemotherapy) complicated by post-splanchnic circulation thromboses or for prevention of intra-hepatic thrombotic syndromes in patients undergoing bone marrow transplantation has been reviewed [105]. Despite increased bleeding and/or thrombosis risks, patients received daily danaparoid doses ranging from 1250 U to 3600 U. In the CUP, the general trend of plasma alanine and aspartate transferases, alkaline phosphatase, and bilirubin in the 74 patients with serial data was toward restoration of normal values during danaparoid treatment, and no toxic effect could be discerned [106]. Also in the Japanese adults and children, these parameters did not reveal any systematic deterioration in these parameters or bleeding problems during or after danaparoid exposure.

Vascular procedures

Danaparoid was only approved for off-line use for vascular procedures if the patient had current or remote HIT. The most frequent requests were for coronary bypass surgery and arterial embolectomy.

Cardiopulmonary surgery with bypass: Danaparoid was requested for cardiopulmonary by-pass surgery (CPBS) due to the high frequency of perioperative HIT. A preliminary animal study [108] suggested that a dosing intensity achieving a plasma anti-Xa activity range of 1.5–2.0 U/mL (i.e. a mean 16,500 U danaparoid) would be sufficient to maintain anticoagulation within the circuit and bubble chamber. The first 91 bypass operations were completed successfully, but 25.3% of the patients developed late re-bleeding after postoperative haemostasis [42]. This was difficult to control in the absence of a specific antidote. Re-operation, multiple transfusions, and prolonged supportive management were therefore often required. Reported approaches to limiting or controlling bleeding included the following:

- protamine sulphate, DDAVP, EACA etc. without effect [42],
- topical fibrin sealant [43,44] and aprotinin [45] prevented bleeding,
- plasmapheresis [44] stopped bleeding by removing danaparoid over a 4-6 h period,
- transfusion of blood products [42] by a combination of diluting the blood and increasing renal elimination of danaparoid slowly stopped blood loss over a 12-24 h period.

A causative relationship with the total dose of danaparoid used was probably confounded by the frequent practice of infusing the patient with residual blood remaining in the bypass machine or in cell savers at the end of surgery. Both sources contain high levels of danaparoid and should not be used for any surgery. An additional factor was the injection of late intraoperative danaparoid 1500 U boluses to control fibrin formation in the surgical field. These would have contributed to the ability of danaparoid to enhance post-operative thrombolysis [20,21]. A revised dosing schedule was therefore introduced with the aim of reducing the need for these additional danaparoid boluses.

In the first 32 patients treated with this revised regimen, the frequency of additional intraoperative boluses fell from 42.9% to 27.6% (p = 0.0307) but the rate of prolonged postoperative bleeding remained similar at 28.1%. A reduction in all-cause mortality (16.0% to 9.4%) was not statistically significant.

In this surgical setting, avoidance of danaparoid is justified because of its perceived bleeding risk in the absence of a clinically validated direct antidote. Danaparoid should only be used if:

- there is no suitable alternative antithrombotic available for CPBS and if for a HIT patient,
- it is not possible to wait three to four months until the HIT-Ab is cleared from the patient's circulation, by whBy which time heparin can again be used.

Danaparoid is safe for post-CPBS thromboprophylaxis [71,106-111] once haemostasis is established, even in the

presence of a large intracranial haematoma [112]. It has also been used in 37 mainly non-HIT patients requiring coronary artery surgery without bypass (OPCAB) [113-115]. However, in the comparative study with heparin [113], in which the latter was immediately reversed with protamine after surgery, mean intra-operative blood loss was similar but post-operatively danaparoid-treated patients developed a higher mean total blood loss (1394 ml v 1130 ml) and required more transfusions. There was no difference in ICU stay or hospital stay between the two treatment groups. The authors considered danaparoid a useful alternative to UFH in patients with HIT who require OPCAB.

Non-cardiac vascular surgery: Danaparoid is safe after peripheral vascular surgery and for non-surgical vascular procedures in a small number of patients (see Tables 6 and 7).

Danaparoid regimens and dosing intensity were the same for HIT and non-HIT patients (but most were HIT patients): either a pre-procedure/pre-operative danaparoid i.v. bolus of 2500 U (3750 U if >90 Kg body weight) only or with a continuous maintenance infusion at 150 – 200 U/h until 30-45 minutes before the end of surgery, if the operation was expected to last many hours. If necessary and provided haemostasis had been restored, danaparoid was restarted six hours post-operatively at the same continuous i.v. infusion for five to seven days.

Table 6: Peripheral Vascular and OPCAB surgery performed with danaparoid.

Types of vascular surgery with danaparoid anticoagulation	CUP & Case reports
Peripheral bypass graft (revision)	24
Embolectomy	57
Endarterectomy	10
Abdominal Aortic aneurysm	4
A-V shunt insertion/revision	5
Hepatic transplant	5
Renal transplant	5
Miscellaneous	12[1]
OPCAB	38
Post-operative course	
Fatal/non-fatal bleeding events	0/6 3.8%
Fatal/non-fatal thromboses	1/7 5.0%

[1] repair of arterial tears causing post-op bleeding and post-PCI femoral pseudoaneurysms; AV: Arteriovenous; OPCAB: Off-Ppump Coronary Artery Bypass

Table 7: Invasive vascular procedures performed during the danaparoid CUP.

Type of invasive vascular procedure	No. of procedures	
	Current HIT	Remote/Non-HIT
PCI	20	19
IABP insertion/removal	21	0
IVCF insertion/removal	14	2
Angiography/catheterization	14	15
Plasma exchange	5	3
Renal artery embolisation	1	0
Pacemaker insertion	1	1
ECMO	1	0
ASD (non-surgical) closure	2[1]	0
Total number of procedures	79	40

ASD: Atrial Septal Defect; ECMO: Extra-Corporeal Membrane Oxygenation; IABP: Intra-Aortic Balloon Pump; IVCF: Inferior Vena Cava Filter insertion or removal; PCI: Percutaneous Coronary Intervention. [1] unspecified coagulation deficit.

All 122 reported peripheral vascular operations performed using danaparoid prophylaxis [CUP, 116-134] were completed. Non-fatal bleeding events comprised incisional haematomas and post-operative haemorrhages (one during follow-up on warfarin due to an INR of 11), only one of which required re-operation. One patient reportedly sero-converted to positive danaparoid HIT-Ab cross-reactivity and developed a new PCR and TE. The fatal TE was a mesenteric thrombosis that developed on warfarin two weeks after danaparoid discontinuation, and one graft re-thrombosis was successfully re-operated at a higher danaparoid dose.

Non-surgical vascular procedures: The majority (105) of the reported 116 patients [CUP, 115, 116, 135-160] undergoing 119 invasive, non-surgical vascular procedures with danaparoid anticoagulation (see Table 7) had current or remote HIT. Most patients received the recommended single pre-procedure i.v. bolus of 2250 U, but for some longer procedures an i.v. infusion was also given.

All procedures apart from four PCIs were completed successfully. One PCI patient died due to an on-table myocardial infarct and six developed non-fatal clotting episodes. Three of the latter led to abandonment of the procedure, and three with clotting beyond the stents responded to switching from prophylactic to therapeutic danaparoid dosing (2) and/or adding a thrombolytic (2). Of six non-cardiac thromboses, three were treated by increasing the danaparoid dosing intensity [116,146,150], one patient developed leg ischaemia and died of endotoxic shock [134], one was a post-partum DVT treated by adding a thrombolytic [140], and one case developed multiple thrombi due to a previously undiagnosed atrial sepAtrial septal defect [142].

Three patients receiving danaparoid treatment for insertion, protection, or removal of an intra-aortic balloon pump (IABP) died of cardiac shock/low output heart failure as or soon after their IABP was removed. Femoral puncture-site tears with bleeding during removal of two IABPs and 3 femoral catheters were surgically repaired using danaparoid.

(Hyper) sensitivity to danaparoid

Many investigators cite its perceived potential cross-reactivity with cation/PF4 antibodies as a reason for not using danaparoid in the management of HIT or VITT.

Pre-treatment cross-reactivity: For both the low-molecular weight heparins (LMWHs) and danaparoid, the reported frequency of pre-treatment serological cross-reactivity depends strongly on the sensitivity and specificity of the assay used. In a review of 2257 archived HIT plasma samples [161], danaparoid cross-reactivity with HIT antibodies was 7.6% overall, with a range of 0% to 50% across individual studies. This compares favorably with a mean of over 50% for the LMWHs. The highest figure came from a small study employing an experimental, highly sensitive fluid-phase ELISA [162]. In more conventional routine HIT assays,

reported cross-reactivity generally ranges from 0% to 23%, with a mode of 0%. When present, danaparoid cross-reactivity was often weak and, in three studies, was still associated with favourable clinical outcomes [162-164].

Residual heparin in patient samples is a plausible explanation for some apparent cross-reactivity [165-171]. Supporting this interpretation, six CUP patients with positive pre-treatment cross-reactivity became negative when retested 24–48 hours later, before danaparoid treatment had started, suggesting that the initial signal may have reflected continued presence of circulating heparin rather than true danaparoid reactivity.

Based on this evidence, HIT experts have advised against routine pre-treatment testing for danaparoid cross-reactivity [172-174], and such testing was not required in recent guidance on HIT management [175,176].

Clinical cross-reactivity: Although positive pre-treatment serological cross-reactivity with danaparoid is unlikely to have major clinical consequences, persistent or recurrent thrombocytopenia, or new or progressive thrombosis during danaparoid treatment, are often assumed to represent clinical cross-reactivity and danaparoid is immediately discontinued. In many cases, however, alternative explanations can explain these events, so before impugning danaparoid cross-reactivity as the cause, the following points should be checked carefully:

Concerning danaparoid:

- the dosing intensity in relation to the thrombotic risk/load of the patient [51,177-179] and safety?
- Is it being administered as a continuous infusion?
- Is the plasma anti-Xa activity within the target range?

Concerning the suspect clinical events:

- Were the patient's limbs adequately surveyed for thrombosis before danaparoid treatment initiation [180]?
- Is a co-medication the cause of the low platelet count – especially chemotherapy, antibiotics (particularly cephalosporins, penicillins and the sulpha group), non-steroidal anti-inflammatory drugs (NSAIDS), cardiac drugs and diuretics, antidepressants, H2-antagonists, antihistamines, anti-epileptics and anti-platelet drugs?
- have all sources of heparin been eliminated, including heparin-bonded lines, catheters and circuits [181]?
- has inadvertent re-exposure to heparin occurred?
- does the patient have hereditary or acquired (especially if hepatic dysfunction is present) AT deficiency? Despite less reliance on plasma AT levels than the heparins, danaparoid's efficacy may be reduced at plasma AT levels <50% of normal [182].

Failure to consider these possibilities may lead clinicians to discontinue what may be the most useful heparin replacement for that patient. By contrast, when similar complications occur during treatment with agents that cannot cross-react with HIT antibodies, such as vitamin K antagonists, direct thrombin inhibitors, or direct oral anticoagulants, they are generally interpreted as treatment failure or progression of HIT rather than as a drug-specific immune reaction.

Other hypersensitivity reactions: In HIT or pre-HIT patients, an immediate Type I anaphylactoid reaction causing fever, flushing, cardio-respiratory problems, hypertension, and chest pain may be observed. This acute systemic reaction (ASR) [183] can be life-threatening if cardiac arrest develops. Danaparoid is reported to have successfully replaced heparin in 18 patients developing an ASR [184-190].

Symptoms and signs of an ASR may complicate haemodialysis heparin anticoagulation; signs and symptoms of an acute systemic reaction (ASR) may develop [191,192], and several patients were switched from heparin to danaparoid [193-198]. Repeat of the same reaction on danaparoid was interpreted as cross-reactivity leading to its discontinuation. However, it proved to be a hypersensitivity reaction to ethylene oxide sterilization of the HD circuit or to the polysulphone/polyethersulphone dialysis membranes, and heparin or danaparoid anticoagulation could be resumed.

Skin reactions to heparin may complicate HIT in 10-20% of cases or develop spontaneously [199]. These and other hypersensitivity reactions often led to danaparoid replacement of heparin. For skin hypersensitivity, a cross-reactivity test with danaparoid was usually performed, and if positive, danaparoid was avoided or discontinued if already started.

Rarely, a necrotic isolated Type III Arthus reaction/phenomenon at or remote from injection sites may develop within a few days of heparin treatment initiation [200]. Thrombocytopenia is often absent despite the presence of HIT antibodies. This localised reaction can be caused either by immune complex-induced local vasculitis resulting in skin ischaemia and/or by HIT-antibody-induced thromboses in small dermal blood vessels. Isolated skin necrosis was the reason for danaparoid use, particularly in pregnancy. Switching from heparin or some direct thrombin inhibitors to warfarin may also precipitate a severe necrotic skin reaction. This happens because already low Protein C levels rapidly reduce further, as warfarin inhibits its hepatic synthesis faster than that of fibrinogen, thereby increasing the risk. Danaparoid is unlikely to be associated with this type of necrosis because it has only a weak antithrombin effect and thus maintains adequate Protein C levels, and has a longer antithrombotic effect. Hence, no problem has been reported with the transition of danaparoid to a vitamin K antagonist.

Most danaparoid requests, however, have been for Type IV delayed-type hypersensitivity (DTH). The inconsistency between the various methods used: patch, prick, scratch tests, or intra-dermal/sub-dermal injections, etc., led to much inter-subject variation, and at least one test was positive if two or more methods were employed. It typically presents as an irritating or painful maculopapular injection site reaction that increases in intensity with repeated exposure. The lesions may become indurated or necrotic, can spread beyond the injection site, and may confound the choice of anticoagulant therapy. Virtually all patients who were switched to danaparoid did not have HIT, and in most, the rash developed during pregnancy. These patients had either negative skin cross-reactivity test(s) or were untested. It is interesting to note that several pregnant patients with severe heparin-induced reactions received danaparoid without prior skin testing and developed tolerance, i.e., successive subcutaneous injections produced a progressively milder reaction until, by days five to seven, it failed to re-appear [161]. Furthermore, some skin reactions could be alleviated by switching from s.c. to i.v. administration [205,201-204] or by local application of a steroid [209,210].

A spontaneous new skin reaction among the 810 CUP cases developed in six patients during danaparoid exposure, but only one remained unexplained after consideration of alternative causes, e.g. heat rash or sensitivity to telemetry patches, antibiotics (2) or benzoic acid.

Danaparoid immunogenicity

Concern is sometimes expressed about possible danaparoid-induced antibody formation, but this appears highly unlikely because danaparoid lacks the known structural requirements of a PF4-binding glycosaminoglycan [1,205] and, uniquely, it interferes with key steps in HIT pathogenesis [22-24,205]. Long-term use for up to 12 years has not been associated with loss of efficacy or safety. In addition, repeated danaparoid exposure in 72 CUP patients, with intervals ranging from 6 days to 775 weeks with a median of 6 weeks, did not appear to reduce efficacy or safety. If anti-danaparoid HIT-like antibodies do arise spontaneously, the available evidence suggests that they are clinically inactive.

Outcomes of danaparoid use for its Approved indications

DVT Prophylaxis: During development of danaparoid for DVT prophylaxis, more than 2000 patients were studied, with approximately equal numbers of men and women and an age range of 18–95 years. These studies showed that 750 U administered subcutaneously twice daily was the most effective regimen, producing statistically significant reductions in total and proximal DVT, with reported risk reductions ranging from 26% to 86% and 40% to 100%, respectively.

Across medical and surgical studies, the frequency of major bleeding with danaparoid was similar to or lower than that observed with active comparators even when danaparoid was started pre-operatively. Only with placebo was the bleeding frequency lower. No consistent relationship was seen between plasma anti-Xa activity and major bleeding in either prophylaxis or treatment studies. More recent controlled studies in Japan have evaluated danaparoid for DVT prophylaxis after various types of surgery [52-57]. Table 8 compares the pooled outcomes of these studies with the surgical studies used for danaparoid marketing approval [85-88,206-208].

Thrombotic and bleeding event rates in Japanese subjects follow the same trend as those reported in predominantly Caucasian populations. The levels of frequency of VTE and post-operative blood loss between the two population samples (Table 8) probably reflect:

- the difference in timing and intensity of dosing regimens used – in Japan 1250 U i.v. once or twice daily (in one study 750 U i.v., b.d. [53]) starting post-operatively and in non-Japanese studies 750 U s.c., b.d. starting pre-operatively.
- the types and duration of surgery – in Japan mainly caesarean section with some gynaecological cancer and benign surgery, in non-Japanese studies a predominance of hip surgery and major cancer surgery.

However, overall the results support the view that race does not materially influence the efficacy or safety of danaparoid.

Heparin-induced Thrombocytopenia (HIT)

In inflammatory states, protective cationic chemokines such as platelet factor 4 (PF4), neutrophil-activating peptide-2, and interleukin-8 are released into the circulation in large amounts. Heparin, a strongly anionic molecule, forms complexes with several of these proteins, particularly PF4. If stoichiometric concentrations allow, ultra-large complexes can form [205], which may induce platelet-activating antibodies, predominantly of the IgG class. If these antibodies are not neutralised by endogenous protective mechanisms, they

Table 8: Pooled results of VTE prophylaxis (surgical studies).

	Japanese studies[1]			Non-Japanese studies[2]		
Study end-points	Dan	Other[3]	None/ IPC	Dan	Other[4]	Placebo
N	535	136	324	1104	1027	99
VTE[5]	3.0%	11.8%	13.8%	15.6%	23.8%	56.6%
Major bleed[5]	0.7%	3.7%	0.0%	3.9%	4.1%	0.0%
Haematoma[5]	0.5%	8.0%	0.0%	1.0%	2.1%	0.0%
Post-op blood-loss (ml)[5]	403	352	232	527	472	700[6]

[1] caesarean section, hip surgery, gynaecological surgery.
[2] hip and cancer surgery trials used for danaparoid marketing approval
[3] UFH & LMWH
[4] UFH ± dihydroergotamine, LMWH, warfarin, dextran,
[5] Studies missing an endpoint were not included in the calculation for that endpoint.
[6] Data only available for 1 study [Hoek]

drive the thrombocytopenia, increased thrombin generation, and thrombosis characteristic of classical HIT [209]. Similar antibody-mediated mechanisms have been described in delayed-onset HIT (dHIT) [210,211], spontaneous/autoimmune HIT (aHIT) [212], and in some patients with COVID-19 or vaccine-induced thrombotic thrombocytopenia (VITT). In dHIT, polyanions other than heparin may complex with PF4, whereas in aHIT, COVID-19, and VITT, heparin may also complex with cell-free DNA released during severe tissue injury or infection [213].

Preclinical HIT studies with danaparoid

Several observations support the suitability of danaparoid for HIT treatment. These include its:

1. lack of heparin [2],
2. low molecular weight [1]
3. low overall charge density compared with the heparins [1]
4. lack of binding or release of PF4 after i.v. injection [9,10]
5. inability to form the ULCs with PF4 required for HIT-Ab induction [1,214]
6. ability to prevent platelet activation by heparin in the presence of the HIT-Ab [22,23]
7. unique ability among approved antithrombotics to interfere with the binding of the heparin: PF4 IgG to its targets [24].

Actions six and seven occur most clearly at therapeutic danaparoid concentrations and suggest that danaparoid may interfere with the pathogenesis of HIT rather than merely replace heparin anticoagulation. Although the isolated HA-HS fraction can bind HIT antibodies [23], this interaction is completely reversed when the pentasaccharide-free NA-HS fraction is added back in the ratio (11:1 w/w) present in whole danaparoid. This 'protective' action has practical implications because the two HS subfractions have markedly different elimination half-lives. With intermittent twice-daily subcutaneous or intravenous dosing, the protective NA-HS fraction may be largely cleared before the next dose, thereby reducing both antithrombotic and immune-modulatory activity and potentially leaving HA-HS relatively unshielded. For this reason, continuous intravenous infusion after an initial loading bolus may better preserve the functional balance between HA-HS and NA-HS in patients with current HIT, unless the clinical situation requires another approach. This regimen has been associated with greater efficacy [215] and faster platelet count recovery than prophylactic dosing [216]. If continuous infusion is not feasible, more frequent subcutaneous administration (for example, 750 U three or four times daily) may be considered, although it may be less effective.

Clinical HIT Studies with danaparoid

The clinical course of HIT can be divided into three main phases [217]: acute HIT, in which thrombocytopenia and anti-platelet antibodies are both present; subacute HIT, in which antibodies persist after platelet count recovery; and remote HIT, in which antibodies are no longer detectable by routine laboratory methods. For treatment purposes in this review, acute and subacute HIT are grouped as "current HIT", because the presence of circulating HIT antibodies in both phases is associated with a high thrombotic risk that requires therapeutic danaparoid dosing intensity. About one week after platelet count recovery, the dosing level can generally be reduced to prophylactic intensity or transitioned to an oral anticoagulant until antibodies become undetectable. Anticoagulation can then be discontinued unless the patient's clinical condition dictates otherwise. Furthermore, for patients with special requirements – for renal dialysis support, surgery, and invasive procedures specific dosing regimens are available [51].

When HIT is suspected, all sources of heparin should be stopped immediately, including catheter flushes and heparin-bonded vascular access devices, and replaced where necessary with heparin-free alternatives. This instruction should be communicated clearly to the entire care team to avoid inadvertent re-exposure. Delay in recognising HIT or in switching to an alternative anticoagulant substantially increases the risk of serious thrombosis, and reported mortality may reach 30%. For this reason, an alternative antithrombotic should be started before laboratory confirmation is available; if testing is negative, the original heparin can be resumed. Persistent thrombocytopenia beyond 72 hours is not, by itself, a reliable indicator of HIT, particularly in intensive care patients with a comorbidity or concomitant drugs that can also cause thrombocytopenia and/or thrombosis. Diagnosis should therefore be based on the '4Ts' clinical score together with HIT-specific laboratory testing. A negative rapid immunoassay [218] is useful for excluding HIT and avoiding unnecessary interruption of heparin. If positive, confirmation should ideally be obtained with a platelet activation assay and/or an immunoassay specific for IgG anti-PF4/heparin antibodies [219].

Danaparoid was first reported as a successful treatment for HIT in 1982 [220]. A compassionate-use programme (CUP 1981-1997) was established that enrolled 656 patients with current HIT, 92 with remote HIT, and 62 without HIT, ranging in age from infancy to 100 years. This CUP had no exclusion criteria, so many patients were critically ill, in intensive care, had renal or hepatic dysfunction, and many required vascular surgery or other interventions. HIT was confirmed in 74% of the CUP patients by either functional serology (66%) or by a positive clinical indicator of HIT (8%), such as white clot

syndrome or recurrent thrombocytopenia during repeated heparin exposures, particularly in patients undergoing intermittent haemodialysis. Since then, it has become an established option for HIT management.

A summary of CUP outcomes together with independent case reports (1478 in total) showed acceptable efficacy and safety of danaparoid across a broad range of medical and surgical patients [161]. HIT mortality in treated CUP patients was also significantly lower than in patients who were enrolled but did not receive danaparoid because of delivery problems (10.9% *vs.* 24.4%; Fisher's exact test P = 0.0010). Those patients instead had received aspirin, dextran, low-molecular-weight heparin, a vitamin K antagonist, or no replacement antithrombotic therapy. This publication also reported an 8.12% rate of major bleeding overall. The highest major bleeding frequency, 26.0% (32/123), was associated with cardiopulmonary surgery with a bypass machine. In all other reported surgical settings, the frequency of major bleeding was 3.6% (109/2987).

A prospective randomised study comparing danaparoid with dextran in well-characterised acute HIT [222], together with historical comparisons against other heparin alternatives [215,222-224], supported regulatory approval for HIT treatment. Indirect comparison between the danaparoid-versus-ancrod study [215] and studies used for the approval of two direct thrombin inhibitors [224-227] suggested favourable composite efficacy, defined as all-cause mortality plus non-fatal thromboembolic events, while danaparoid was the only agent reported to be significantly safer than its study controls.

Advice for HIT management with danaparoid

Taken together, the available evidence suggests that clinically relevant danaparoid cross-reactivity with HIT antibodies is uncommon. On that basis:

- pre-treatment danaparoid cross-reactivity testing is unnecessary but:
    - if a test is performed, then do not wait for the result to initiate danaparoid treatment,
    - if a test result is positive for danaparoid cross-reactivity but danaparoid has already been started, then it should not be automatically discontinued, especially if the platelet count is recovering.
- it is advisable to check the platelet count daily during the first week of danaparoid treatment, on alternate days during the second and third weeks of treatment, and regularly with decreasing frequency thereafter if treatment continues,
- if the platelet count has shown no increase and/or a new thrombotic event has occurred after 72 hours of therapeutic danaparoid treatment and other causes have been eliminated, then danaparoid should be immediately discontinued. However, a positive cross-reactivity test is required to support a claim of danaparoid cross-reactivity.

Disseminated Intravascular Coagulation (DIC)

Sepsis, inflammatory disorders, acute tissue injury, and cancer are all commonly associated with disseminated intravascular coagulation (DIC), a syndrome in which haemostatic regulation is profoundly disturbed.

Although associated predominantly with sepsis, other causes are:

- major damage to organs or tissues, e.g. hepatic cirrhosis, pancreatitis, severe trauma, burns, major surgery, brain injury.
- severe immune reactions following failed blood transfusion, organ transplant rejection or toxins, e.g. snake venoms.
- serious pregnancy-related problems including abruptio placenta, retained placenta, amniotic fluid embolism or severe bleeding during or after delivery.
- various forms of cancer, particularly haematogenous malignancy
- large haemangiomas, e.g. Kasabach-Merritt syndrome (KMS).

In DIC, disruption of the normal cross-talk between coagulation and immunity drives both thrombotic and inflammatory injury, especially in sepsis-related disease. The resulting abnormalities in haemostasis and endothelial function can lead to systemic thrombosis, microvascular fibrin deposition, and bleeding. Organ failure is common, and the high mortality, typically ranging from 20% to 50%, appears to be inversely related to the presenting plasma AT level [228-232]. Because factor Xa generation may amplify inflammatory responses in DIC [233], adequate AT levels appear to be clinically important. Therefore, supplementation or treatments that preserve or enhance AT activity and/or inhibit factor Xa generation or thrombin generation are often considered in DIC management. However, use of anticoagulants other than AT remains controversial in DIC [234-238]. This is because heparins may reduce AT levels and interfere with protective antithrombin–endothelium interactions [5,240] and may increase the bleeding risk, especially in fibrinolysis-dominant forms of DIC. Even so, anticoagulation has been associated with reduced mortality in some settings [235,238].

Preclinical DIC studies

In vitro studies and animal models in mice and rats showed that danaparoid can prevent or attenuate inflammation

and acute injury induced by septic shock, endotoxin, lipopolysaccharide, platelet-activating factor, cerulein, heat stress, and ischaemia/reperfusion [19,20,26,241-248], and can also prevent or treat DIC [249,250]. The high- and no-AT-affinity components together inhibit thrombin generation, and both appear to contribute to protection in endotoxin-induced DIC [241-248]. Intact danaparoid was more effective than heparin in ameliorating endotoxin-induced DIC and was as effective as, but less haemorrhagic than, unfractionated heparin or dalteparin in tissue factor-induced DIC. In a pilot study in healthy volunteers, therapeutic danaparoid dosing also attenuated lipopolysaccharide-induced inflammation and coagulopathy [21].

Clinical experience in DIC patients

In the first clinical study of danaparoid for DIC, 14 patients with acute promyelocytic leukaemia and multisite bleeding related to marked fibrinolysis received chemotherapy together with danaparoid. Outcomes of the first four patients [64] and the remaining ten patients [manufacturer data on file] suggested that, despite a high mean dose of 6500 U/day (approximately 270 U/h by intravenous infusion) for up to 14 days, bleeding was controlled by day seven. Early plasma anti-Xa activities occasionally exceeded 1.0 U/mL, but maintenance levels were generally below 0.8 U/mL, including in two patients with persistent acute promyelocytic leukaemia who later died from cerebral haemorrhage on treatment days 10 and 11. No other adverse events were reported during danaparoid treatment or during the 3-month follow-up. Danaparoid also reduced soluble fibrin, PAI-1, and D-dimer more effectively than heparin in ICU patients with sepsis-related DIC [251], and combined use with AT appeared more effective than either agent alone [25,249,252].

Of the 208 patients in Japanese pre-approval studies, 64.3% were males and 48.1% were >65 years of age. Treatment outcomes at 10 days revealed marked/moderate DIC improvement (resolution or clinically significant improvement) in 75% of leukaemic patients compared with 56.7% of non-leukemic patients. Overall mortality was 34%, with most patients dying of underlying causes. One PE occurred – treated by doubling the dose of danaparoid, and two major bleeds were reported, one fatal and the other managed by halving the danaparoid dose. Based on these results, danaparoid was approved in Japan for DIC treatment with a dosing regimen of 1250 U o.d. or b.d., i.v. boluses.

Table 9 presents pooled analyses of baseline characteristics, danaparoid treatment, and major outcomes in 1902 patients with DIC identified from the literature [25, 258-289] and a post-marketing surveillance (PMS) study with sufficient data for analysis. All 'pre-approval' cases, PMS cases, and most non-HIT cases were Japanese, whereas only five of the patients with current HIT were treated in Japan. In the PMS cohort, intermittent danaparoid injection appeared least effective in patients with severe DIC, renal or hepatic failure, severe bleeding, or severe organ failure. By contrast, continuous danaparoid infusion, used mainly outside Japan in patients with current HIT, appeared more effective, although that population also carried high baseline mortality.

Table 9: Patients with DIC/coagulopathies exposed to Danaparoid.

Patient stratification		Japan Pre-approval	Current HIT[1]	Non/remote HIT	Japan PMS
n		208	91	209	1393
Gender[2]	Male	64.3%	39.6%	59.5%	49.4%
	Female	35.7%	60.4%	40.5%	50.6%
Daily dose[3]	≤2250 U inter	21.7%	13.3%	1.9%	0
	≤2250 U infus	0	0	2.1%	0
	≥2500 U inter	78.3%	10.8%	83.8%	100%
	≥2500 U infus	0	75.9%	12.3%	0
DIC causes[4]	Sepsis/infection	20.0%	27.5%	70.0%	39.2%
	Leukaemias	35.2%	35.9%	37.1%	14.7%
	Solid tumours	39.0%	15.4%	37.6%	19.3%
	Other[5]	5.7%	50.5%	7.1%	46.8%
Organ Failure (at least one organ)		No data	11.0%	26.7%	33.6%
Treatment Outcomes	DIC response[6]	66.3%	75.8%	80.1%	54.5%
	DIC unresponsive[7]	33.7%	13.2%	19.9%	45.5%
	Major bleed	1.0%	5.5%	3,3%	4.0%
	Thrombosis	0.5%	6.6%	0.0%	0.13%
	28-day Mortality	16.3%	24.2%	16.2%	4.8%[8]

[1] These patients also presented with a coagulopathy frequently described as DIC
[2] percentages of 86 HIT cases, 113, 79 HIT, on/past HIT cases, and 1477 PMS cases.
[3] percentages of 189 pre-approval subjects, 143 non/past HIT cases, and 1507 PMS cases
[4] more than 1 possible (particularly sepsis and cancer) but only known for 104 pre-approval subjects
[5] early post-operative, aortic disease, arterial thrombosis,
[6] DIC resolution described as complete, marked, improved or resolving
[7] DIC slightly/non-responsive or worse
[8] 73 deaths of the total 3379 PMS (post-marketing surveillance) patients (DIC + non-DIC) enrolled, but calculation based on DIC cohort only.
Inter: Intermittent injections once or twice daily i.v. (a few s.c.), infus: continuous infusion regimen.

Overall, in non-HIT patients danaparoid:

- appears most useful for acute coagulation-dominant DIC associated with leukaemias, solid cancers and relapsing/chronic DIC [255-258]. The DIC response of leukaemic patients compared with non-leukaemic cases was respectively 60.8% vs 53.4% in the PMS study and 75.0% vs 56.7% in pre-approval studies.
- produced DIC resolution in leukaemic patients more rapidly but not more frequently than the serine protease inhibitors gabexate mesylate (FOY) and nafamostat mesylate (Futhan), particularly in patients with refractory underlying disease [258].
- was used successfully to treat fibrinolysis-dominant DIC associated with APL [64], giant haemangiomas, i.e. Kasabach-Merritt syndrome (KMS) [259-262], aortic aneurysm dissection [263-267] and breast angiosarcoma [257].
- Combination with tranexamic acid [252,263,266,268] or a serine protease inhibitor [269-272] enhanced efficacy outcomes.

- Compared with rTM [273-275], danaparoid was as or less effective in the treatment of septic DIC. Successful combination with rTM is described [282-284] and also danaparoid use following rTM failure [283].

The KMS cases [259-262] involved three females and one male. The DIC in two of these patients responded immediately to a combination of danaparoid 1250 U i.v. b.d. and tranexamic acid, in one patient after addition of gabexate mesylate, and the fourth patient to danaparoid alone. After successful DIC resolution, two patients underwent irradiation therapy for a haemangioma [259] and a scalp angiosarcoma [260], one underwent resection of a retroperitoneal haemangioma [261], and the fourth had her hepatic haemangioma removed by partial hepatectomy at 16 weeks of pregnancy [262]. All patients recovered with danaparoid treatment for one to five months.

Discussion

With this review, the authors wish to ameliorate long-standing concerns about danaparoid use. These largely stem from contraindications and warnings agreed for marketing approval (pre-2000) at a time of adverse experience with other anticoagulants (warfarin, heparin and the first generation LMWHs) or when too little data on danaparoid was available. Since then, despite new data, the many license holders of danaparoid have not updated this information in the danaparoid package insert.

To address this, we have provided new insights into its pharmacology, a central point being that, unlike frequent claims, there is no so-called 'half-life of danaparoid', only the half-lives of its components and their measured activities. Thus the 24.5 h elimination of its effect on plasma anti-Xa activity is only mediated by the 4% (by weight) HA-HS component that contributes to only 50% of the antithrombotic activity of intact danaparoid. The half-life of the effect of danaparoid on TGI integrates the effects of all its active components and, from animal studies, aligns with the half-life of intact danaparoid's antithrombotic effect. It seems reasonable to assume that this also holds for man. This means that its clinical effects in thrombosis prevention require twice daily dosing for optimal efficacy. This is important because a long half-life is quoted as a reason for avoiding danaparoid, and inappropriate and underdosing are the major causes of danaparoid treatment failure.

Danaparoid treatment is too frequently set aside by potential users because of fears of bleeding induction or exacerbation (particularly in patients requiring surgery or with renal and/or hepatic failure) and cross-reactivity (in patients with various forms of HIT and other pathological disorders associated with anti-PF4 antibodies. The requirement for surgery (e.g. amputations and vascular surgery) is common in HIT patients and organ dysfunction is a frequent complication in DIC. Without the benefit of randomised comparative studies, information on danaparoid use in the clinical situations that include the restrictions to its use has come from a large compassionate-use programme for patients with heparin intolerance (mainly HIT), off-label comparative studies and single and multiple case reports that have been published since marketing approval. Virtually all of the data on DIC and supporting use in the presence of severe hepatic failure has come from Japan, and few articles are available in the English literature. Thus is order to show that this data applies elsewhere, we have compared PK and clinical study outcomes of Caucasian and Japanese patients. We conclude from these data that there are no clinically relevant differences in the handling of danaparoid by the two races; therefore, data from one can be extrapolated to the other. This applies to cross-reactivity, bleeding propensity, use in renal and hepatic failure, and in pregnancy and children. Although prospective head-to-head comparisons with current antithrombotics are lacking, the large body of evidence available provides valuable insight into real-world use of danaparoid, even if case reports are not generally considered to offer the same level of evidentiary certainty as randomised trials. Taken together, the available data continue to support the efficacy and safety of danaparoid when it is dosed according to recommended guidance [51] despite persistent concerns about the absence of a validated antidote.

After considering the clinical outcomes of danaparoid use, the authors have some suggestions for improving its efficacy.

Danaparoid dosing

One of the main reported causes of danaparoid treatment failure is underdosing [177,179,222]. Often, even in the presence of thrombosis, danaparoid is administered twice daily by subcutaneous injection to patients with current HIT and DIC. This is occasionally related to fears of bleeding or underestimation of the thrombotic risk in the patient. The pathogenesis of these and other immune-thrombotic disorders (catastrophic antiphospholipid syndrome, vaccine-associated thrombocytopenia and thrombosis, etc.) is driven by increased thrombin production and high levels of pathological (auto)immune antibodies. Optimal management of these problems requires the constant presence of the two main active components of danaparoid in the proportions found in intact danaparoid. This can only be provided by a continuous therapeutic infusion since with intermittent injections there is increasing dissociation between the levels and hence activities of the NA-HS and the HA-HS due to their widely different elimination rates (6.7 h v 24.5 h respectively). Thus, by the time of the next injection of a twice-daily schedule, the NA-HS fraction has almost disappeared from the circulation, leaving the HA-HS fraction unprotected late in the dosing interval [30]. This leaves the patient vulnerable to an increased thrombotic risk and loss of the anti-inflammatory/immune modulatory effects of the NA-HS fraction for significant fractions of the day. We propose

therefore that for immune-thrombotic disorders, particularly in the acute stages, danaparoid should be administered at therapeutic intensity by continuous infusion [51] to maintain optimally interactive levels of its active components. This proposal is supported clinically in HIT patients by lower rates of composite inefficacy outcomes in indirect comparisons with argatroban and hirudin [215] and faster platelet count recovery [216], without compromising safety. Furthermore, many current HIT patients developing a new thrombosis responded favorably to replacing their intermittent dosing schedule with a (higher daily dosing intensity) continuous infusion.

Danaparoid cross-reactivity

Danaparoid is currently the only approved antithrombotic that treats HIT in addition to its thrombotic complications because it uniquely interferes with the interactions of heparin/PF4 complexes and the specific anti-platelet HIT antibody that drive the pathogenesis of HIT [22-24]. Despite this and although danaparoid is neither clinically immunogenic nor able to form the ultra-large PF4 complexes required for classical HIT pathogenesis, clinicians often suspect cross-reactivity when platelet counts fail to recover and/or when new thrombosis develops during treatment. The possibility of cross-reactivity is also frequently cited as a reason for avoiding danaparoid. Even if it occurs subsequent clinical cross-reactivity is very unlikely [162-164] and the few cases reported fail to mention alternative causes.

In the CUP and later post-approval use, the most plausible explanations for events attributed to cross-reactivity were underdosing [177,179,215], comorbidity especially sepsis, concomitant heparin exposure [161,181,290] and AT deficiency [185,285]. In the absence of these possibilities, persistent thrombocytopenia or thrombosis is more likely to reflect ongoing HIT than true danaparoid cross-reactivity, especially since they occur as or more frequently with non-immunogenic heparin alternatives [228]. While clinical cross-reactivity does not appear to influence danaparoid's overall efficacy or safety, it is regrettable that no systematic study has been performed.

DIC

Preclinical studies from Japan showed that danaparoid could attenuate systemic inflammation, coagulopathy, and organ injury, and early clinical studies in DIC were encouraging. Later clinical experience, however, has been mixed [245,246,281-286]. As a result, danaparoid is now mentioned only sparingly in recent DIC guidance [234,236,239], despite many successful case reports.

An analysis of treatment outcomes of 2,715 individual DIC cases exposed to danaparoid (2,599 from Japan) with sufficient treatment outcome data reveals several factors that may explain this gap between expectation and practice. First, DIC is biologically heterogeneous, and the balance between thrombosis, fibrinolysis, inflammation, and organ failure likely influences which therapies are most effective. Second, many comparative studies relied on historical controls and were vulnerable to selection bias and time-related changes in background care. Third, and potentially most important for danaparoid, is that in much of the Japanese clinical literature the locally approved intermittent dosing regimen of 1250 U once or twice daily intravenously for DIC is cited and in practice often reduced further. However, intermittent dosing is inappropriate for high thrombotic risk situations and a 1250 U i.v. injection, especially twice daily, is likely to further increase the risk of bleeding [8] because of the higher post-injection spikes of danaparoid. We propose therefore that since there do not appear to be any racial differences in the pharmacokinetic handling of danaparoid, similar to acute HIT patients, danaparoid for DIC treatment should be administered by continuous i.v. infusion delivering 2400-4800 U/day). This daily infusion rate may need to be adjusted in patients with significant renal impairment or outside the body weight range of 55 – 90 Kg [51]. The target plasma anti-Xa range for this dosing regimen is 0.4-0.8 U/mL, but unfortunately, monitoring of plasma anti-Xa activity has not been reported for Japanese patients. This proposal is biologically plausible, and although supported indirectly by prior clinical experience and the results of COVID-19 and VITT treatment, it still requires prospective safety and dose-finding validation.

Chronic DIC can be more conveniently treated with subcutaneous danaparoid, and patients have learned to self-inject at home, thus avoiding the need for repeated outpatient clinic visits.

Skin reactions

A positive skin test indicating danaparoid cross-reactivity does not necessarily preclude safe, long-term rash-free danaparoid treatment, since tolerance has been observed to develop [109]. Unfortunately, the frequency of developing tolerance to danaparoid has not been systematically investigated, and in practice 22.4% of the skin reactions treated with danaparoid led to its discontinuation as a result of recurrence after the first injection. It is recommended therefore to at least persist with danaparoid injections unless the rash worsens or fails to respond to local or systemic steroids. If either occurs, danaparoid must be switched to a non-sensitizing alternative.

Danaparoid Contraindications and Warnings

Many of the contraindications and warnings attached to danaparoid appear to be overly conservative in selected circumstances, but this ideally requires confirmation in proper safety, dose-setting and comparative studies. This is especially important in HIT and DIC treatment where many severely ill patients present with at least one restriction to danaparoid use. It has been safe and effective in severely bleeding patients with promyelocytic leukaemia [64] or in renal failure, with acute spinal cord injury and in the TOAST

study [295]. IN this last study, more than 600 patients received continuous therapeutic danaparoid infusions within 24 h of an ischaemic stroke for seven days, despite which haemorrhagic transformation occurred at a similar rate to placebo. Additional reports in recent haemorrhagic stroke [58], and VITT with intracranial thrombosis and bleeding [60] also support danaparoid use in such high-risk patients.

Another example is the contraindication to danaparoid use in severe renal or hepatic insufficiency unless the patient has HIT and no alternative is available. However, the CUP of 802 patients did not show a systematic deterioration in renal or hepatic laboratory indices, even among those with abnormal values at baseline. In addition, published reports describe successful danaparoid use in non-HIT patients undergoing HD [41], CVVRT [72] if recommended precautions to avoid accumulation are followed [51]. In Japan, treatment for portal vein thrombosis in the setting of advanced hepatic dysfunction, cirrhosis, or hepatoma [108] has also been successful in over 1500 patients (and may be further improved if, like treatment of thromboembolism elsewhere, intermittent injections are replaced with the continuous infusion regimen).

These observations do not remove the need for caution, but they suggest that absolute avoidance as a response to the contraindications and warnings for danaparoid use may not always be warranted or best for the patient.

Unofficial warnings

For danaparoid use in patients undergoing CPBS and continuous arteriovenous renal replacement therapy (CAVRRT), an unofficial warning is in place. Although danaparoid use for CPBS itself appears to be successful, severe post-operative re-bleeding occurs at a similar rate as after heparin use. In the absence of a validated antidote (despite some potential candidates [16,48,49]) it the bleeding is difficult to control. Major bleeding during CAVRRT from the arterial puncture site is also difficult to control. Therefore, the manufacturer does not generally recommend danaparoid use for either setting.

Conclusion

Overall, danaparoid appears to remain a safe and effective antithrombotic for its approved indications of DVT prophylaxis, HIT and DIC, even when these are complicated by clinical problems that are contraindications and warnings to its use.

Studies in Caucasian and Japanese healthy volunteers and patients in renal failure suggest that danaparoid metabolism and elimination from the circulation are not materially influenced by age, sex or race. Hence, results of studies in one group of patients can be extrapolated to the other.

A recurring clinical problem is inappropriate danaparoid dosing despite the availability of clear dosing instructions. For disorders where both antithrombotic and anti-inflammatory effects are likely to matter—particularly current HIT and some forms of DIC—therapeutic-intensity danaparoid administered as a continuous intravenous infusion after an initial bolus may offer the most appropriate pharmacologic strategy. This recommendation requires prospective validation.

For routine venous thrombosis prophylaxis, the approved subcutaneous injection schedule is recommended over intravenous bolus injections.

Author contributions

All authors contributed to the development and review of this manuscript. They met ICMJE authorship criteria, approved the final version, and made the final decision regarding submission to this journal.

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Dr. Harry Magnani was the principal clinical developer of danaparoid for its original manufacturer, Organon BV. From 2013-2021, in retirement, he provided information on danaparoid to the companies owning its marketing license: Schering-Plough and Aspen Pharma. Since 2021, he has no affiliation with and receives no support or funding from any source.

Prof. PD Dr. med Stanislava *Tzaneva* has no conflict of interest.

Availability of data and materials: The report for the DIC post-marketing surveillance study (PMS) in Japan 2003-2006 is not publicly available, but the corresponding author was granted a copy that can be shared.

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