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Desirudin

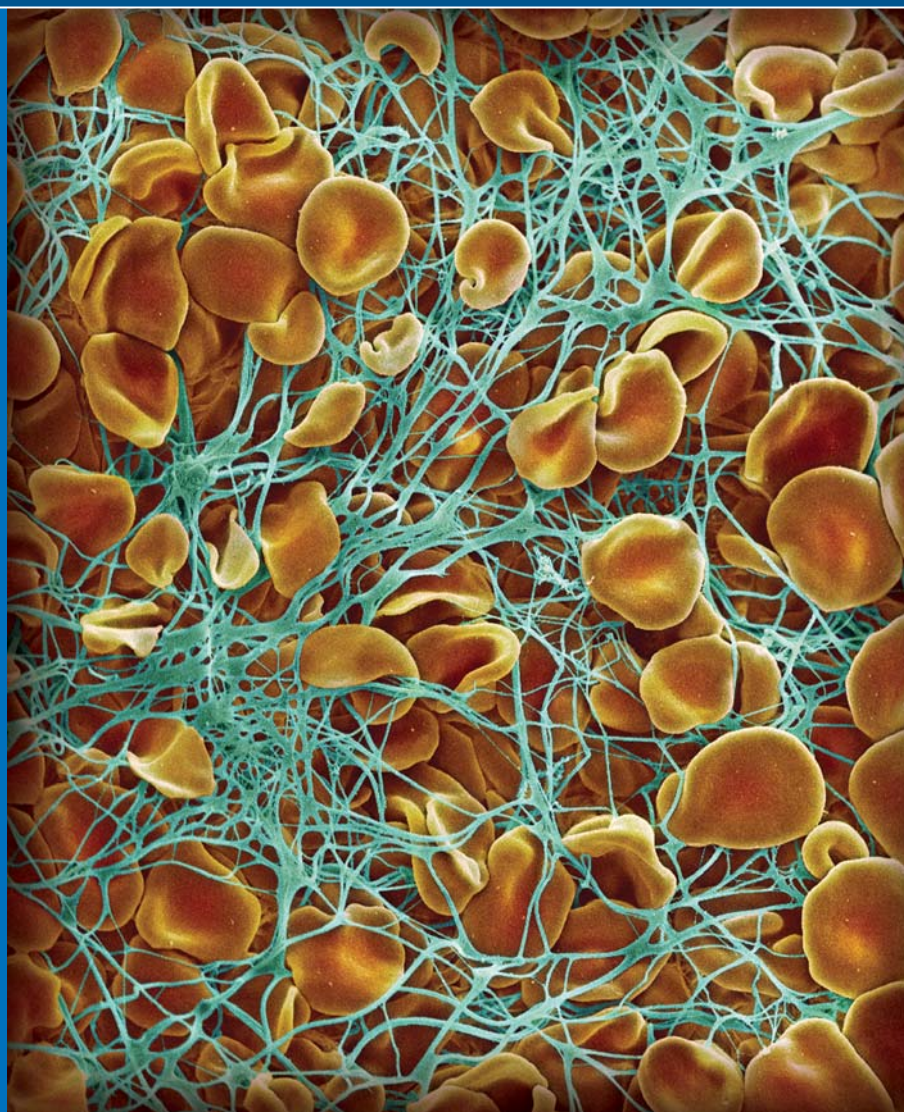
A Summary of Recent Data in Patients With or
at Risk for Heparin-Induced Thrombocytopenia

Jerrold H. Levy, MD, FAHA

Department of Anesthesiology
and Critical Care
Emory University School of Medicine
and Emory Healthcare
Atlanta, Georgia

Jeanine M. Walenga, PhD

Cardiovascular Institute
Loyola University Medical Center
Maywood, Illinois



President,
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Jerrold H. Levy, MD, FAHA
Department of Anesthesiology
and Critical Care
Emory University School of Medicine
and Emory Healthcare
Atlanta, Georgia



Jeanine M. Walenga, PhD
Cardiovascular Institute
Loyola University Medical Center
Maywood, Illinois

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Desirudin: A Summary of Recent Data in Patients With or at Risk for Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a life-threatening, prothrombotic, immune-mediated coagulopathy caused by antibodies that bind to macromolecular complexes of heparin and platelet factor 4 (PF4).^{1,3} The antibody-mediated platelet activation that occurs as PF4 binds to heparin releases prothrombotic microparticles.³

HIT can occur with any route of heparin administration.⁴ According to the current American College of Chest Physicians Guidelines for treatment and prevention of HIT, thrombocytopenia in HIT is defined as a fall in the platelet count of more than 50%, occurring 5 to 14 days after beginning heparin therapy,⁵ although it may occur earlier in some patients with previous occult exposure.^{5,6} In other patients (3%–5%), thrombocytopenia does not begin to occur until several days after heparin therapy has been discontinued.^{5,7}

Incidence of HIT

An estimated 8% to 50% of patients treated with heparin develop heparin/PF4 antibodies,⁸ and HIT occurs in approximately 0.2% to 5.0% of heparin-treated patients.^{5,9-11} The incidence of HIT depends on the heparin preparation (unfractionated heparin [UFH] > low-molecular-weight heparin [LMWH]), the patient population type (eg, postsurgery, medical, pregnant), whether patients are critically ill, the duration of heparin exposure, and sex.⁵

The patient groups at highest risk for HIT ($\geq 1\%$) include postopera-

tive orthopedic, cardiac, vascular, and percutaneous coronary intervention patients, who often have multiple exposures to heparin, receive high doses of heparin, or receive heparin for an extended period of time.^{5,12}

HIT is an important cause of hypercoagulability, and thrombotic complications develop in approximately 38% to 76% of patients.¹³ This translates to an estimated 300,000 patients with HIT-related complications and 90,000 deaths per year in the United States.¹⁴

Costs of Treatment

HIT is costly. Total annual costs in the United States when HIT complicates open-heart surgery are estimated at \$300 million.¹⁵ An economic analysis from the Complications After Thrombocytopenia Caused by Heparin (CATCH) registry was conducted to assess the incremental impact of thrombocytopenia on in-hospital costs among 1,988 patients receiving heparin for at least 96 hours.¹⁶ Thrombocytopenia was defined as (1) an absolute reduction in platelet count of less than $150 \times 10^9/L$ ($n=353$), (2) a relative reduction in platelet count of more than 50% from admission levels ($n=41$), or (3) as meeting both criteria ($n=185$). Patients in all three categories had significantly longer hospital stays and greater medical costs than did the group without thrombocytopenia. The differential was greatest in the thrombocytopenia group that met both criteria. In that group, the average length of hospital stay was 22.3 days, and average hospi-

tal costs were \$61,760, compared with 13.0 days and \$23,154 for patients without thrombocytopenia ($P<0.001$).

Diagnosis of HIT

Diagnosis is based on both clinical and serologic findings. Thrombocytopenia or thrombosis and heparin-dependent antibodies are needed to confirm the diagnosis.⁵ Clinical suspicion of HIT should arise when any of the following occurs in association with the presence of heparin-dependent antibodies: (1) an otherwise unexplained platelet count fall of at least 30% to 50%, even if the platelet count nadir remains above $150 \times 10^9/L$; (2) venous or arterial thrombosis; (3) skin lesions at heparin injection sites; or (4) acute systemic reactions (eg, fever/chills, tachycardia, hypertension, dyspnea, cardiopulmonary arrest) that occur after intravenous (IV) heparin bolus administration.^{5,17}

The diagnosis of HIT can often be challenging, given the frequent use of heparin and the common occurrence of thrombocytopenia arising from other causes in the hospital setting, such as perioperative hemodilution, multiorgan dysfunction syndrome, sepsis, and immune-mediated thrombocytopenia caused by other medications (eg, quinidine, rifampin, vancomycin, and sulfa antibiotics).¹⁸ Nonpathogenic heparin/PF4-reactive antibodies frequently occur in patients who have recently received heparin; a positive test for heparin-dependent antibodies does not necessarily mean that a patient has HIT.¹⁸

Once HIT is strongly suspected or confirmed, heparin should be immediately discontinued, and alternative methods of anticoagulation should be initiated, whether or not thrombosis is present.^{1,5} In patients with isolated HIT who are not treated or who are treated with warfarin alone, the risk of thrombosis ranges from 23% to 52%, with a 5% risk of fatal thrombosis.¹⁹ Also, warfarin monotherapy should be avoided in this situation, owing to its delayed time to full onset and to associated risks of skin necrosis and venous gangrene in the limbs.²⁰ Initiation of appropriate therapy should not wait for laboratory confirmation, as the standard turnaround time for confirmatory laboratory testing for heparin-dependent antibodies can be as long as 3 days.³ Treatment of HIT requires use of non-heparin-based anticoagulants, such as direct thrombin inhibitors (DTIs) or, potentially, other agents, such as fondaparinux, to reduce the risk of thrombosis in these patients.^{1,5}

Direct thrombin inhibitors are considered a mainstay of treatment for HIT.^{5,21} Desirudin is a potent, highly selective DTI that exhibits predictable pharmacokinetics when administered as a fixed-dose, subcutaneous (SC) injection. An effect on activated partial thromboplastin time (aPTT) is observed within 30 minutes, and maximum plasma drug concentrations are reached within 3 hours after SC administration of desirudin.²²⁻²⁴ It is more effective than UFH and LMWH for deep venous thrombosis (DVT) prophylaxis in patients undergoing hip-replacement surgery,^{25,26} and is the only DTI approved for venous thromboembolism (VTE) prophylaxis by SC injection. Based on the results of the PREVENT-HIT study, desirudin shows promise as a potentially cost-effective alternative to argatroban in patients with suspected HIT, with or without thrombosis.²⁷

Novel data on the use of desirudin in various patient populations with confirmed or suspected HIT were recently presented at several medical society meetings and are summarized here.

Overview of the PREVENT-HIT Study

The PREVENT-HIT trial was an open-label, exploratory study designed to assess the clinical and economic utility of a twice-daily fixed dose of SC desirudin given to prevent thrombosis in critically ill patients with suspected HIT (with or without thrombosis), compared with a continuous infusion of aPTT-adjusted argatroban. The details of the methodology and results of this study were recently reported^{27,28} and are briefly summarized here.

Sixteen adult patients in whom HIT was clinically suspected were randomized to one of two treatment arms (group A or B). Eight patients who had not previously received treatment with a DTI were assigned to group A; of these, four patients received desirudin, and four patients received argatroban. Group B included eight patients who were already being treated with argatroban before study entry. Of these, four patients continued to receive argatroban, and four patients were randomized to desirudin.

Patients assigned to desirudin who did not have clinical evidence of thrombosis received 15 mg SC every 12 hours (n=7); those with thrombosis at study entry received desirudin 30 mg SC every 12 hours (n=1). Argatroban was administered via IV infusion and titrated to a therapeutic aPTT according to the standard of care at each study center. Patients were transitioned to warfarin once their platelet counts exceeded 100 to 150 x 10⁹/L. The main efficacy measure was the composite of new-onset or worsening thrombosis requiring discontinuation of study medication, amputation, or all-cause mortality up to 30 days after discontinuation of study medication. Descriptive statistics were used to describe all data collected. Incidence of major and minor bleeding and of pharmacoeconomic outcomes was also assessed. Major bleeding was defined as a fall in hemoglobin of more than 2 g/dL requiring transfusion; all other bleeding was classified as minor. One patient in group B receiving desirudin withdrew consent and discontinued participation on day 5 of treatment, but all 16 patients were included in efficacy and safety analyses.

Patient demographics and baseline characteristics for the overall population and for the subgroup with

TABLE 1. PREVENT-HIT Patient Demographics and Baseline Characteristics

Characteristic	OVERALL COHORT		CONFIRMED HIT	
	Desirudin (n=8)	Argatroban (n=8)	Desirudin (n=5)	Argatroban (n=6)
Mean age, years ± SD (Q1, Q3)	69.0 ± 9.5 (62, 76)	62.0 ± 9.3 (53, 70)	67.2 ± 9.0 (59, 73)	61.3 ± 9.0 (53, 67)
Gender male, n	5	5	3	4
Mean weight, kg ± SD (Q1, Q3)	81 ± 22 (64, 99)	100 ± 37 (64, 130)	84 ± 15 (74, 96)	105 ± 39 (68, 132)
Baseline platelet count (x10 ⁹ /L) ± SD (Q1, Q3)	88 ± 40 (63, 124)	121 ± 68 (84, 137)	107 ± 29 (82, 132)	129 ± 77 (94, 148)
Renal function, CL _{cr} ± SD (Q1, Q3)	50 ± 19 (37, 64)	58 ± 25 (42, 77)	53 ± 21 (37, 67)	57 ± 26 (43, 69)
Moderate or severe renal impairment, n	5	4	3	3

CL_{cr}=creatinine clearance measured in milliliters per minute, Q1=quartile1, Q3=quartile 3.

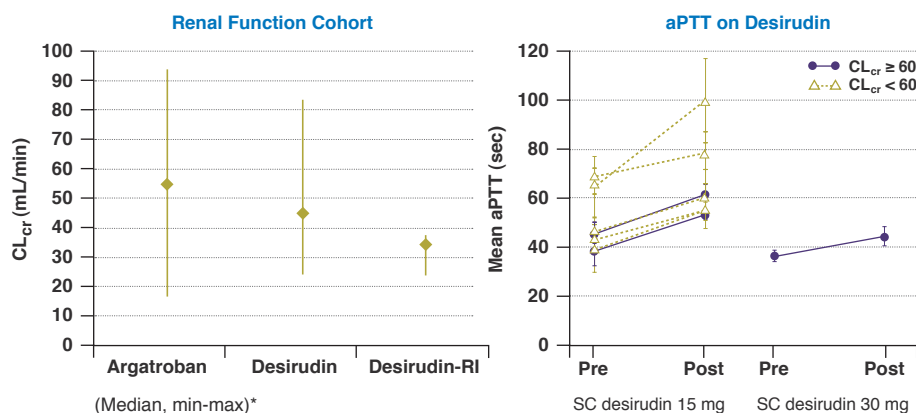
Source: Boyce et al²⁷

confirmed HIT are summarized in **TABLE 1** on page 4. Renal impairment was defined as creatinine clearance (CL_{cr}) below 60 mL/min. On average, patients assigned to desirudin were older, had lower body weight, and had a lower platelet count at baseline than patients treated with argatroban. In the primary analysis, no differences were observed in thrombotic outcomes or in the incidence of bleeding between desirudin and argatroban.

PREVENT-HIT Renal Impairment Subanalysis

Desirudin is primarily eliminated via renal mechanisms.^{21,24} The current US Food and Drug Administration (FDA)-approved prescribing information for desirudin recommends a reduction in dosage from 15 mg SC every 12 hours to 5 mg SC every 12 hours in patients with moderate renal impairment (CL_{cr} 39–59 mL/min/1.73 m²) and to 1.7 mg SC every 12 hours in patients with severe impairment (12.1–27.2 mL/min/1.73 m²).²⁹ This recommendation is based on data from a single-dose IV study that compared total exposure (area under the curve [AUC]) in patients with renal impairment and in healthy volunteers.³⁰ However, data from two recent analyses—one assessing clinical outcomes in total hip replacement and the steady-state pharmacokinetics of desirudin 15 mg SC every 12 hours for up to 6 days, and another evaluating clinical outcomes in patients with renal impairment undergoing major orthopedic surgery and treated with desirudin 15 mg twice daily or enoxaparin 40 mg daily—suggest that dose reduction of desirudin in patients with moderate renal impairment is not warranted.^{31,32} These data are being submitted to the FDA for review to determine if recommendations in the current prescribing information for patients with renal impairment should be modified. Since desirudin is

FIGURE 1. Left Panel: Median Creatinine Clearance Rates in the Overall Argatroban and Desirudin Groups, and Renally Impaired Patients Treated With Desirudin; Right Panel: aPTT Changes in Patients Treated With Desirudin, Stratified by Creatinine Clearance Rates



aPTT=activated partial thromboplastin time, CL_{cr} =creatinine clearance, RI=renal impairment, SC=subcutaneous.

* Median data are shown. Vertical bars represent minimum to maximum data values observed.

Source: Duncan and Kurz³³

eliminated by the kidneys, and renal impairment is common in critically ill patients, a subgroup analysis was performed on the PREVENT-HIT data set to evaluate the efficacy and safety of desirudin at standard fixed doses in patients with renal impairment.³³ Median CL_{cr} rates for the overall argatroban and desirudin groups, as well as the subgroup of patients with renal impairment who received desirudin, are shown in the left panel of **FIGURE 1**. Changes in aPTT levels in desirudin-treated patients stratified by CL_{cr} are shown in the right panel.

Efficacy and safety outcomes for the overall desirudin and argatroban groups, and for the subgroup of patients with renal impairment treated

with desirudin, are summarized in **TABLE 2**. Patients with moderate renal impairment (CL_{cr} 30–60 mL/min) did not experience exaggerated increases in aPTT with fixed-dose desirudin, and moderate renal impairment was not associated with excess bleeding.

PREVENT-HIT Health Economics Subanalysis

Another analysis of the PREVENT-HIT data set was conducted to investigate differences in resource utilization and economic outcomes between the desirudin and argatroban treatment groups.³⁴ A summary of medication costs, duration of treatment, and length of hospital stay for each treatment group is presented in **FIGURE 2** on page 6.

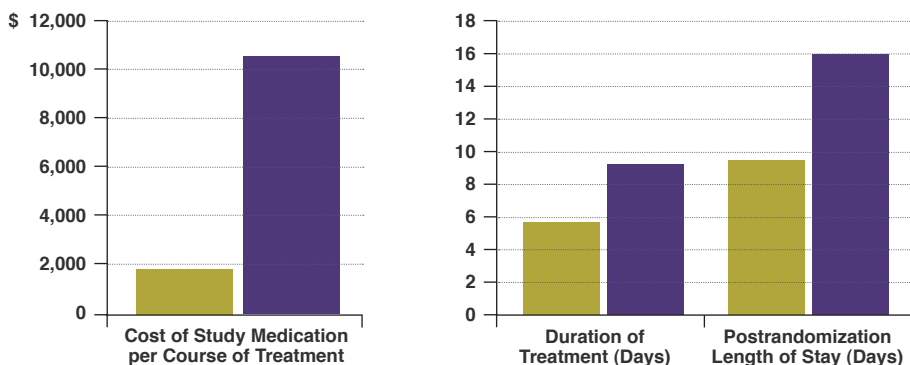
TABLE 2. PREVENT-HIT Efficacy and Safety Endpoints

	Argatroban (n=8)	Desirudin (n=8)	Desi-RI (n=5)
Median CL_{cr} , (min–max)	56 (18–94)	46 (24–83)	36 (24–37)
New thrombosis, amputation, or death	0	0	0
Major bleed	2	0	0
Minor bleed	1	1	0

CL_{cr} =creatinine clearance measured in milliliters per minute, Desi-RI=desirudin patients with renal impairment, min=minimum, max=maximum.

Source: Duncan and Kurz²³

FIGURE 2. Key Cost Drivers



■ Desirudin ■ Argatroban

Source: Frame et al³⁴

Data on the transition from desirudin and argatroban to warfarin in patients with confirmed HIT is presented in **FIGURE 3**.

The mean cost of medication per course of treatment was \$1,991 for desirudin and \$10,230 for argatroban, with an average savings of \$8,239 (range \$2,288–\$15,325) per patient treated with desirudin. Patients receiving desirudin had a shorter mean treatment (5.9 days) and a shorter mean postrandomization length of stay (9.4 days) than did patients treated with argatroban (9.3 and 16 days, respectively). Patients on desirudin who

had confirmed HIT (n=5) required an average of 1.8 fewer days of warfarin overlap (4.6 days), compared with argatroban (n=6, 6.4 days). Patients with confirmed HIT and treated with desirudin who were transitioned to warfarin (n=5) had an average of 5.0 international normalized ratio (INR) tests compared with 8.7 INR tests for argatroban patients (n=7).

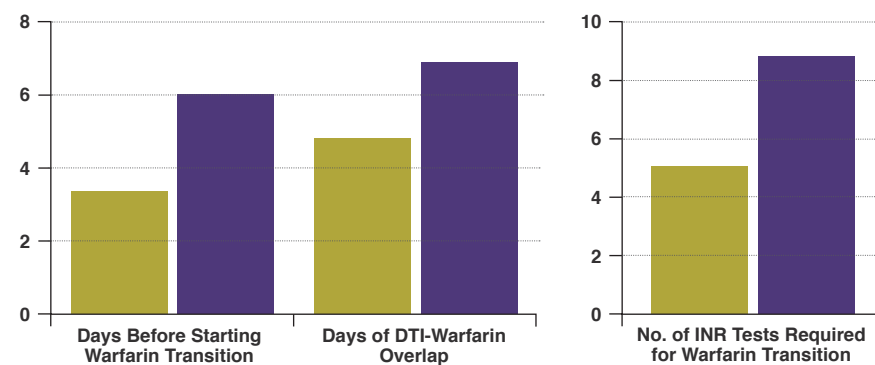
Perioperative Use of Desirudin in Patients With and Without HIT Undergoing Orthopedic Surgery: The DESIRE Registry

DVT is an important complication in

patients undergoing major orthopedic surgery, and routine pharmacologic thrombosis prophylaxis is recommended for most patients in this setting.³⁵ There are few alternatives to heparin-based anticoagulants for surgical patients who are not candidates for heparin therapy (eg, patients with HIT or a history of HIT). The Desirudin Post-Marketing Registry–Europe in Patients Undergoing Major Orthopedic Surgery (DESIRE Registry) was an observational, multi-center, single-arm registry that enrolled 603 patients undergoing major orthopedic surgery.³⁶ All patients received desirudin 15 mg SC twice daily and were followed and evaluated for DVT, pulmonary embolism (PE), bleeding, and death throughout their hospital stay. Of the 581 patients included in the overall analysis, 303 (52.2%) underwent hip replacement, 196 (33.7%) total knee replacement, 39 (6.7%) hip-fracture repair, and 43 (7.4%) other types of surgery (eg, spinal or trauma). Patient characteristics are summarized in **TABLE 3** on page 7. The mean duration of treatment with desirudin was 11 days; 28.3% of the patients received desirudin for more than 12 days. Desirudin was given prior to surgery in 50.3% of the patients and after surgery in 48.8% of the patients. A summary of clinical outcomes that occurred during hospitalization is presented in **TABLE 4** on page 7.

A subanalysis of the DESIRE Registry that included 51 patients who had clinical HIT (n=14; 6 were confirmed with serology) or a history of HIT (n=47; 37 did not have HIT during the indexed period) evaluated the efficacy and safety of desirudin in this high-risk subset.³⁷ Of the patients with clinical HIT, none died or experienced a thrombotic event; there was one reported major bleeding event, but cessation of desirudin treatment was not required. Of the patients with a history of HIT, one patient developed DVT after receiving 1 dose of desirudin, and

FIGURE 3. Patients Confirmed With Heparin-Induced Thrombocytopenia



■ Desirudin ■ Argatroban

DTI=direct thrombin inhibitor, INR=international normalized ratio.

Source: Frame et al³⁴

TABLE 3. DESIRE Registry Patient Characteristics

Characteristic	Patients (N=581)
Mean age, years ± SD	67.9 ± 5.0
Mean duration of desirudin therapy, days ± SD	11 ± 6.6
BMI >30 kg/m ² , %	30.0
Medical history, %	
3 risk factors for DVT, not including orthopedic surgery	66.7
Prior DVT	35.0
Prior PE	9.8
Post-thrombotic syndrome	13.0
Malignancy	10.0
Diabetes	17.0
Congestive heart failure	33.0
Tobacco usage	17.0

BMI=body mass index, DVT=deep venous thrombosis, PE=pulmonary embolism.

Source: Puente et al³⁶

TABLE 4. DESIRE Registry: Summary of Clinical Outcomes

Outcome, n (%)	Patients (N=581)
Confirmed venous thrombotic event	11 (1.9)
Deep venous thrombosis	8 (1.4)
Pulmonary embolism	3 (0.5)*
Desirudin discontinued due to bleeding	5 (0.86)

*Includes one fatal pulmonary embolism after an emergent spinal surgery due to trauma.

Source: Puente et al³⁶

six patients experienced major bleeding. Desirudin was not discontinued in any of these cases. The patient with DVT was switched to heparin for unknown reasons and 10 days later developed a symptomatic DVT confirmed with phlebography.

Few venous thrombotic events occurred in this population of orthopedic surgery patients, and the incidence of bleeding was low in the overall population. The incidence of bleeding was also low in the subgroup of patients with HIT. However, interpretation of the results is limited by the observational nature of the study.

It is important to note that all anticoagulant medications, including DTIs such as desirudin, are associated with an increased risk of bleeding and should be used cautiously.

Perioperative Use of Desirudin in Patients With Heparin Antibodies Undergoing CABG

Results from previous observational studies suggest that antibodies to heparin/PF4 complexes are prevalent in patients undergoing cardiac surgery.^{38,39}

In these studies, the presence of heparin/PF4 antibodies before surgery was a significant, independent risk factor for increased perioperative morbidity and mortality. Anticoagulation and VTE prophylaxis during the perioperative period, while avoiding heparin with the use of a DTI, may improve outcomes in these patients.

A prospective observational study was conducted to evaluate the efficacy and safety of desirudin in patients undergoing elective coronary artery bypass graft (CABG) surgery who were positive for heparin antibodies at baseline but had no clinical evidence of HIT.⁴⁰ Desirudin 15 mg SC was administered twice daily preoperatively and postoperatively, for VTE prophylaxis. Bivalirudin IV was administered for anticoagulation during surgery. Outcomes measured included thrombosis, major bleeding, and development of clinical HIT.

A total of 28 patients were enrolled. Desirudin was administered to 18 patients preoperatively and to 24 patients postoperatively. On average, 3 doses of desirudin were given preoperatively, with the last dose given at 8:00 P.M. on the evening before surgery. Treatment with desirudin was reinitiated within 12 hours after surgery in three of the patients, within 12 to 24 hours in eight patients, and longer than 24 hours after surgery in seven patients. The results of this study are summarized in **TABLE 5**. One thrombotic event was reported, occurring about 30 days after the last dose of desirudin. No major bleeding events and no cases of clinical HIT were reported after surgery.

TABLE 5. Results of the Desirudin Study in Patients With Heparin Antibodies Undergoing Coronary Artery Bypass Graft

	Patients (N=28)
Patients with CL _{cr} <60 mL/min	14
Patients with CL _{cr} ≥60 mL/min	14
Patients with postoperative HIT	0
Major bleeding events	0
Thrombotic events	1

CL_{cr}=creatinine clearance, HIT=heparin-induced thrombocytopenia.

Source: Levy and Koster⁴⁰

Summary and Conclusions

Diagnosis of HIT can be challenging given the extensive use of heparin in the hospital setting and the common occurrence of thrombocytopenia due to other causes. Whenever there is a clinical suspicion or confirmed diagnosis of HIT, heparin should be discontinued immediately, and alternative methods of anticoagulation should be initiated pending laboratory confirmation.

DTIs are a mainstay of treatment for HIT. Argatroban has the broadest indication in the United States; it is approved for both prophylaxis and treatment of thrombosis in patients with HIT.⁴¹ However, it must be administered intravenously; must be closely monitored using aPTT or activated clotting time⁴¹; has a substantial effect on INR, which may complicate the transition to oral therapy^{21,41}; and is costly.

Desirudin also exhibits predictable pharmacokinetics when administered at a fixed dose but does not require routine monitoring when it is given for thrombosis prophylaxis or treatment.²⁹ It has less effect on INR than does argatroban^{42,43} and is the only DTI approved for SC injection. Based on the study results described here, desirudin may be a cost-effective alternative to argatroban. Further clinical studies in the setting of HIT are warranted. ■

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