to 38 years, 7 males and 1 female; 7 with dilated cardiomyopathy [DCM], 1 with myocarditis) and they were weaned from LVAS after 89 to 310 days (recovery group: Group R). Thirty-three patients were supported by LVAS for >1 year. They remained generally stable, but they could not be weaned from LVAS because of poor native heart function (non-recovery group: Group N). This group comprised 22 males and 11 females, ages 16 to 55 years, and whose etiologies were as follows: 27 had DCM; 3 were in the dilated phase of hypertrophic cardiomyopathy (dHCM); and 3 had secondary cardiomyopathy (sarcoidosis, myopathy and drugs). Of these, 15 patients underwent heart transplantation, 13 died (6 cerebral hemorrhages, 1 cerebral infarction, 6 infections), and 5 remain on the waiting list. Another 3 patients were weaned from LVAS due to cerebral events despite insufficient natural heart recovery. LVAS support was discontinued within 1 year in the other 35 patients because of transplantation or death.

In Group R, 3 patients were given a Toyobo LA LVAS, 4 a Toyobo LV LVAS and 1 a Novacor device. In Group N, 30 patients were given a Toyobo LV LVAS and 3 a HeartMate VE device. We retrospectively evaluated the differences between Group R and Group N. To assess natural heart function, we followed-up echocardiographic parameters and the brain natriuretic peptide (BNP) levels at 1 and 3 months after LVAS implantation. Medical therapy regimens were also evaluated. The investigations complied with the principles outlined in the Declaration of Helsinki. The study was approved by the institutional review board of the National Cardiovascular Center, and all patients provided written informed consent.

Management After LVAS Implantation

After general stabilization, we re-administered a β-blocker (carvedilol), an angiotensin-converting enzyme inhibitor (ACE-I, enarapril) and an aldosterone antagonist (spironolactone).

The maximum titrated doses were 20, 5 and 25 mg, respectively. The criteria by which we introduced or increased these drugs were as follows: systolic blood pressure >80 mm Hg; heart rate >60 beats/min; and no sign of deterioration of heart failure. Adequate rehabilitation was also combined with medical treatments. Nutritional states were assessed and the patients received nutritional intervention if necessary. The pump rate was gradually reduced to 60/min when cardiac function showed no deterioration.

Weaning Protocol

Device explantation was considered if the patients met the following criteria: left ventricular diameter in diastole (LVDd) <55 mm; fractional shortening (FS) >20%; and BNP < 100 pg/ml under minimal LVAS support (60 pumps/min). Candidates for LVAS explantation then underwent dobutamine stress testing. Dobutamine was titrated from 5 to 40 μg/kg/min, and hemodynamic and echocardiographic data were evaluated at each dose level. The test outcome was classified as favorable if the patients showed an increase in cardiac output and FS with an increase in dobutamine, without an increase in pulmonary capillary wedge pressure (PCWP), LVDd and symptoms of heart failure. Those who responded appropriately to dobutamine stress testing were considered candidates for LVAS explantation.

Statistical Analysis

We used Student's unpaired *t*-test to compare continuous variables (all data expressed as mean ± SD) and the chi-square test to compare categoric variables. In time-course analysis (Figure 1), data were analyzed by 2-way analysis of variance (ANOVA) followed by Tukey's post hoc test. $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS software (version 14-J).

RESULTS

Before LVAS Implantation

Table 1 summarizes the demographics and baseline characteristics of Groups R and N. Group R was significantly younger and had a shorter duration of heart failure than Group N ($p < 0.01$, respectively). Group R had less myocardial fibrosis than Group N ($p < 0.01$). Myocardial hypertrophy tended to be milder in Group R, but the difference did not reach statistical significance. The ratio (%) of patients with dilated cardiomyopathy was similar in both groups. Hemodynamic parameters, echocardiographic parameters, dose of intravenous inotropic agents, ratio (%) of patients supported by percutaneous mechanical assist devices, BNP levels, and degree of other organ dysfunction or anemia did not significantly differ between the two groups. The regimens of medical treatment did not significantly differ between the two groups (Table 2), but the percentage of patients who were given an ACE-I, a β-blocker, a spironolactone or an amiodarone tended to be higher in Group N.

One Month After LVAS Implantation

Echocardiographic parameters (Dd and FS) and BNP levels were more favorable in Group R, but the differences were not statistically significant (Table 3). The ratio (%) of patients who tolerated treatment with a β-blocker was significantly higher in Group R ($p < 0.05$) (Table 4).

Three Months After LVAS Implantation

FS was significantly higher, and BNP levels was significantly lower ($p < 0.05$ and $p < 0.01$, respectively) in Group R than in Group N (Table 5). Furthermore, the

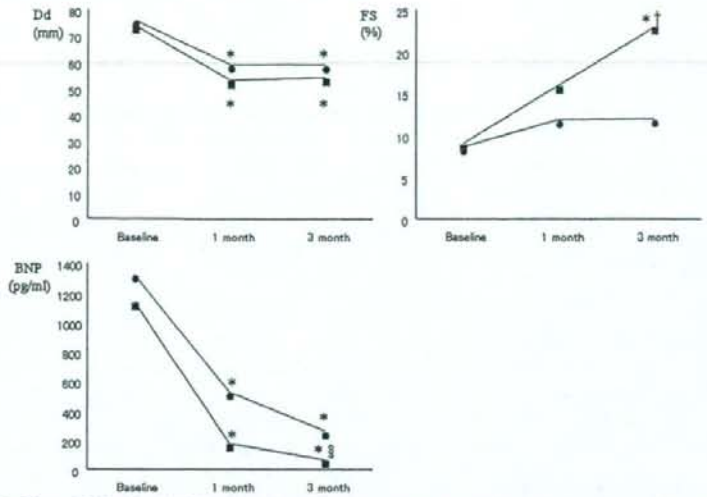

Figure 1. Changes in Dd, FS and BNP after LVAS implantation. Filled squares: Group R; filled circles: Group N. $^{*}p < 0.05$ vs baseline, $^{\dagger}p < 0.05$ vs Group N and $^{\S}p < 0.01$ vs Group N. LVDd, left ventricular end-diastolic dimension; FS, fractional shortening; BNP, brain natriuretic peptide.

increasing rate of FS and the decreasing rate of BNP (3 months after vs before LVAS implantation) were significantly higher in Group R ($p < 0.05$, respectively, data not shown). The dose of β-blocker was higher in Group R ($p < 0.05$) (Table 6). More patients tolerated treatment with an ACE-I or a β-blocker, and Dd tended to be smaller in Group R, but statistical significance was not demonstrated.

Time Course After LVAS Implantation

Figure 1 shows changes in Dd, FS and BNP after LVAS implantation. Improvement of Dd was almost complete

Table 1. Demographics and Baseline Characteristics of Study Population

	Group R ($n = 8$)	Group N ($n = 33$)	p-value
Age (years)	23.4 ± 7.1	36.7 ± 12.4	<0.01[a]
Gender (% female)	12.5	35.3	0.21
Etiology (% dilated cardiomyopathy)	87.5	79.4	0.6
Duration of heart failure (month)	13.3 ± 22	56.1 ± 52	<0.01[a]
Myocardial fibrosis (score)	1.4 ± 0.5	2.5 ± 0.6	<0.01[a]
Myocardial hypertrophy (score)	1.7 ± 0.5	2.2 ± 0.8	0.1
Dose of inotropic agents (DOA + DOB)	9.7 ± 5.6	10.2 ± 4.8	0.83
Use of mechanical support (% IABP and/or PCPS)	62.5	67.6	0.78
Systolic blood pressure (mm Hg)	93 ± 9.0	86 ± 12	0.16
Heart rate (bpm)	116 ± 13	103 ± 25	0.19
Cardiac output (liters/min)	3.21 ± 1.0	3.36 ± 1.0	0.77
Pulmonary capillary wedge pressure (mm Hg)	27.2 ± 4.3	27.2 ± 8.5	0.1
Right atrial pressure (mm Hg)	14.2 ± 5.8	10.2 ± 6.1	0.17
Left ventricular diastolic dimension (mm)	74.1 ± 8.9	75.9 ± 11	0.66
Fractional shortening (%)	9.0 ± 3.7	8.6 ± 4.6	0.84
Wall thickness (mm)	7.6 ± 0.4	7.4 ± 1.4	0.7
B-type natriuretic peptide (pg/ml)	1,140 ± 660	1,282 ± 1,074	0.76
Total bilirubin (mg/dl)	2.6 ± 1.0	1.8 ± 1.0	0.06
Creatine (mg/dl)	1.1 ± 0.5	1.4 ± 1.1	0.52
Hemoglobin (g/dl)	11.4 ± 2.5	10.5 ± 1.8	0.31

Myocardial fibrosis or hypertrophy was classified as mild, moderate or severe and scored as follows: 1 = mild; 2 = moderate; 3 = severe. Dose of inotropic agents is shown as the sum of dopamine (DOA) + dobutamine (DOB). Wall thickness is shown as the mean of the septum and posterior wall. IABP, intra-aortic balloon pump; PCPS, percutaneous cardiopulmonary support.

[a]Statistically significant.

Table 2. Medical Regimens Before LVAS Implantation

	Group R	Group N	*p*-value
ACE-I (%)	37.5	55.9	0.35
β-blocker (%)	12.5	47.1	0.07
Furosemide (%)	100	82.4	0.2
Spironolactone (%)	25	55.9	0.12
hANP (%)	37.5	23.5	0.42
Amiodarone (%)	12.5	50	0.05
Digitalis (%)	37.5	29.4	0.66

Ratio (%) represents drug induction rate. LVAS, left ventricular assist system; ACE-I, angiotensin-converting enzyme inhibitor.

within 1 month in both groups. Augmentation of FS continued during the follow-up period in Group R, but was complete at about 1 month in Group N. BNP levels decreased during the first month and continued to decrease thereafter in both groups.

Prognosis of Patients After LVAS Explantation

Table 7 shows prognosis of patients after LVAS explantation. Three of 8 patients have continued to maintain normal ventricular function during follow-up periods ranging from 8 months to 8 years. Four patients developed recurrent but mild heart failure, and were treated in the outpatient clinic for up to 10.5 years. All are being given an ACE-I (enarapril, mean dose 3.75 mg) and a β-blocker (carvedilol, mean dose 16 mg). The other patient did well up to 8 to 9 years after LVAS removal, but then had episodes of heart failure that required re-LVAS implantation 12 years after explantation. He is now on the waiting list.

DISCUSSION

This study has demonstrated that: (1) young patients with a short history of heart failure and less myocardial fibrosis are candidates for LVAS removal; (2) patients who can be weaned from LVAS show rapid and persistent improvement of natural heart function; and (3) a β-blocker is a potent agent that can induce LVAS removal.

Several mechanisms about restoration of the natural heart by LVAS have been reported. Wohlschlaeger et al showed that ventricular pressure and volume unloading by LVAS reduces harmful neurohumoral and cytokine stimulation (systemic and local), and decreases myocardial apoptosis.[8] Heerdt et al suggested that LVAS support increases the gene and protein levels of SERCA 2a, normalizes Ca^{2+} handling[9] and improves myocardial contraction. Brodde et al demonstrated an up-regulation of a β-receptor after LVAS support.[10] The regression of myocyte hypertrophy and interstitial fibrosis has been also suggested.[11,12] These effects, which occur as a result of maximal ventricular unloading, lead to functional recovery of the native heart.

Basal cardiac states, however, might influence the process of functional improvement. Histologic analysis has demonstrated that less myocardial fibrosis is one of the predictors of LVAS weaning.[13] This finding was also demonstrated in our study. Furthermore, in the present study, myocardial hypertrophy tends to be less common in patients who could be weaned from the device, but a significant difference was not detected. Our study found that younger patients with a shorter duration of heart failure before LVAS implantation were suitable candidates for LVAS explantation. These features indicate less pre-operative myocardial degeneration. The timing of LVAS implantation is very important. LVAS implantation in necessary before myocardial damage becomes irreversible for restoration of natural heart after LVAS implantation. Cardiac function and dysfunctional severity of other organs before LVAS implantation were not statistically different between Groups R and N.

The process of natural heart improvement might reach completion within 4 to 5 months after device implantation.[14] Continued ventricular unloading be-

Table 3. Echocardiographic Parameters and BNP Levels 1 Month After LVAS Implantation

	Group R	Group N	*p*-value
Left ventricular diastolic diameter (mm)	53.7 ± 12.4	59.5 ± 17.6	0.42
Fractional shortening (%)	16.1 ± 12.7	11.9 ± 7.7	0.43
BNP (pg/ml)	176.8 ± 151.6	526.2 ± 483.8	0.09

BNP, B-type natriuretic peptide; LVAS, left ventricular assist system.

Table 4. Medical Regimens at 1 Month After LVAS Implantation

	Group R	Group N	*p*-value
ACE-I (%)	71.4	41.2	0.14
β-blocker (%)	71.4	26.5	<0.05[a]
Furosemide (%)	85.7	88.2	0.85
Spironolactone (%)	57.1	70.6	0.49
Amiodarone (%)	0	20.6	0.19
Digitalis (%)	57.1	26.5	0.11

Ratio (%) represents drug induction rate. LVAS, left ventricular assist system.
[a]Statistically significant.

Table 5. Echocardiographic Parameters and BNP Levels 3 Months After LVAS Implantation

	Group R	Group N	*p*-value
Left ventricular diastolic diameter (mm)	54.7 ± 11.7	58.9 ± 15.4	0.49
Fractional shortening (%)	23.0 ± 17.1	12.0 ± 9.0	<0.05[a]
BNP (pg/ml)	66.6 ± 46.1	264.6 ± 170.1	<0.01[a]

BNP, B-type natriuretic peptide; LVAS, left ventricular assist system.
[a]Statistically significant.

Table 6. Medical Regimens at 3 Months After LVAS Implantation

	Group R	Group N	*p*-value
ACE-I (%)	85.7	55.9	0.14
β-blocker (%)	85.7	55.9	0.14
β-blocker (mg)	15.4 ± 8.4	5.8 ± 3.9	<0.05[a]
Furosemide (%)	57.1	85.3	0.09
Spironolactone (%)	57.1	70.6	0.49
Amiodarone (%)	57.1	32.4	0.22
Digitalis (%)	57.1	29.4	0.16

Ratio (%) represents drug induction rate. LVAS, left ventricular assist system; ACE-I, angiotensin converting enzyme inhibitor.
[a]Statistically significant.

yond this time frame may induce myocardial atrophy and fibrosis. Farrar et al reported that waiting 50 days would capture half of the patients who would ultimately recover ventricular function followed by successful device removal, and waiting up to 90 days could capture 80% of them.[5] We evaluated several parameters at 1 and 3 months after LVAS implantation. Natural heart function was restored more rapidly and the improvement persisted for longer in the weaned patients (Group R). They recovered completely, essentially within 3 months, and were weaned from LVAS after a mean of 5 months of support. BNP was the first representative indicator of native cardiac recovery, which was followed by echocardiographic improvement. None of the patients in whom restoration of the native heart was not indicated for these periods could be weaned from LVAS. This timing is compatible with the findings of Farrar et al.

Recently, the β-blocker has been recognized as being highly beneficial for patients with chronic heart failure, and is becoming the first-line drug treatment for heart failure.[15-17] However, the effect of a β-blocker in patients with LVAS is unclear. We found here that the ratio (%) of patients who tolerated treatment with a β-blocker at 1 month after LVAS insertion and the dose of a β-blocker at 3 months after device implantation were significantly higher in weaned than in non-weaned patients. This result indicates that a β-blocker is useful in patients with LVAS. Several mechanisms underlying the favorable effects of β-receptor blockage have been suggested. A β-blocker restores the function of the calcium-release channel and improves cardiac muscle performance.[18] It also improves myocardial energetics, attenuates myocardial apoptosis, and abrogates induction of the fetal gene program.[19] These effects ultimately help to prevent and reverse ventricular remodeling. Also, these mechanisms might strengthen restoration of the natural heart induced by LVAS. Our findings directly show the importance of β-blocker treatment in patients with first-time LVAS. The percentage of patients who tolerated treatment with an ACE-I after LVAS implantation was also higher in the weaned group, but the values did not reach statistical significance. Conversely, more patients were given a β-blocker, ACE-I, spironolactone and amiodarone before LVAS implantation in the non-weaned group. This may be dependent on the longer duration of heart failure in those patients.

Study Limitations

The present study has several limitations. First, the population size in this investigation was relatively small because the percentage of patients able to be weaned from LVAS is small. Second, the etiologies of patients are various due to the same reason (we could not focus specifically on DCM patients). Third, we demonstrated the effect of a β-blocker. However, we could not standardize the medical regimens after LVAS implantation. Further examinations on larger numbers of patients with uniform etiology and medical treatments are necessary.

In conclusion, weaning from LVAS might be feasible in selected patients. Adjunctive treatments as well as adequate unloading are important in those who

Table 7. Prognosis After Explanation of the Left Ventricular Assist System

Patient no.	Age (years)	Gender	Left ventricular diastolic dimension (mm)	Fractional shortening (%)	B-type natriuretic peptide (pg/ml)	New York Heart Association class	Current status	Duration after explantation
1	29	M	69	5	124	I	Re-LVAS implantation, in hospital, on waiting list	12 years
2	31	M	66	17	103	II	Well, at home	10 years 5 months
3	33	M	50	28	12	I	Well, at home	8 years
4	44	F	53	36	21	I	Well, at home	5 years 7 months
5	25	M	69	10	548	I	Well, at home	5 years 5 months
6	30	M	72	8	275	II	Well, at home	4 years 1 month
7	19	M	91	12	848	II	Well, at home	3 years
8	26	M	51	31	26	I	Well, at home	8 months

have the capability of natural heart restoration. Further studies on LVAS weaning are desirable.

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Heparin-Induced Thrombocytopenia Clinical Studies and the Efficacy of Argatroban in Japan

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ABSTRACT

Immune-mediated heparin-induced thrombocytopenia (HIT) is a life-threatening side effect of heparin therapy. HIT has been better recognized in Japan since April 2006 when prescribing information on heparin was revised to include HIT. Diagnosis and treatment of HIT in Japan, however, are still problematic because Japanese regulators have not yet approved any laboratory tests or pharmacological intervention for HIT, especially in patients with acute HIT who require surgery with cardiopulmonary bypass (CPB). We report on three specific cases anticoagulated with argatroban for CPB showing the difficulty of anticoagulation management. We review several retrospective studies and a multicenter, prospective cohort study that suggest a lower incidence of HIT in Japan than what is diagnosed in Western countries. This may be due to ethnic factors and/or different clinical practices. We conducted a multicenter, nonrandomized, open-label trial showing the efficacy and safety of argatroban when carefully dosed. From this study we describe a Japanese strategy to diagnose and treat HIT that may be of value elsewhere.

KEYWORDS: Heparin-induced thrombocytopenia, Japanese population, direct thrombin inhibitor, argatroban

An anticoagulant turns procoagulant. Thrombocytopenia is associated with thrombosis but not hemorrhage. These are the fundamental paradoxes of heparin-induced thrombocytopenia (HIT), an immune-mediated, life-threatening side effect of heparin therapy.[1–3] Many articles address the pathology,[4–7] diagnosis,[8–13] incidence,[14–17] and treatment[1,18,19] of HIT in various clinical situations, mainly in Western countries. Here we describe how we currently diagnose and treat HIT in Japan, with the goal of continuously improving patients' outcomes in Japan and abroad.

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Landmarks in Anti-Thrombin Drug Development: The Argatroban Story; Guest Editors, Jeanine M. Walenga, Ph.D., Henri Bounameaux, M.D., and Yasuo Ikeda, M.D.

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CLINICAL SITUATIONS FOR HEPARIN-INDUCED THROMBOCYTOPENIA IN JAPAN

Unfractionated heparin (UFH) is still the most frequently used parenteral anticoagulant in Japan for the following reasons. Low molecular weight heparin is approved by Japanese regulators only for hemodialysis and disseminated intravascular coagulation (DIC). Argatroban is the only direct thrombin inhibitor approved by Japanese regulators for stroke, arteriosclerosis obliterans, thromboangiitis obliterans, and hemodialysis of patients with antithrombin deficiency. But argatroban is not approved for heparin-induced thrombocytopenia (HIT). Other direct thrombin inhibitors (e.g., lepirudin and bivalirudin) are not available in Japan because they are not approved for any indication. Danaparoid sodium and fondaparinux are factor Xa inhibitors approved in Japan for DIC (danaparoid) and the prevention of venous thromboembolism (VTE) in patients undergoing major hip and knee surgery (fondaparinux). Fondaparinux was only approved in April 2007. Thus UFH has been widely administered for anticoagulation in cardiovascular surgery with cardiopulmonary bypass (CPB) and percutaneous coronary intervention (PCI), thromboprophylaxis for the high-risk patients of VTE, and other indications (e.g., hemodialysis, DIC).

Annually in Japan, ~200,000 patients suffer from acute coronary syndrome, and 130,000 patients undergo PCI. In addition, ~40,000 patients undergo cardiovascular surgery, and 30,000 patients begin hemodialysis. Thus at least 200,000 Japanese patients are anticoagulated with UFH every year.

Recognition of HIT as an immune-mediated, life-threatening side effect of heparin therapy has probably improved in Japan since manufacturers' prescribing information (package insert) on heparin was revised to include HIT in April 2006. Yet many physicians in Japan report no experience diagnosing or treating HIT, raising the possibility that physicians often overlook HIT. Diagnosis and treatment may also be impaired by the fact that Japanese regulators have not yet approved either a diagnostic test for HIT or a pharmacological intervention. It may also be that the prevalence of HIT is lower in Japan than in Western countries.

Irrespective of incidence or prevalence, HIT is life threatening, especially when unrecognized or untreated.[1,8,20] Therefore we have conducted several retrospective studies at a single institution and a multicenter, prospective cohort study to clarify the incidence and profile of HIT in Japan.[21] In addition, we have conducted a multicenter, nonrandomized, open-label trial to evaluate the efficacy and safety of argatroban, a direct thrombin inhibitor, in Japanese patients with HIT.[22] Based on these results, we will seek to establish Japanese guidelines for the diagnosis and treatment of HIT.

HEPARIN-INDUCED THROMBOCYTOPENIA IN OUR INSTITUTION

The National Cardiovascular Center in Osaka, Japan, is one of the leading institutes for cardiovascular diseases in the country. We perform ~1300 cardiovascular surgeries and 900 PCI procedures each year, making our hospital one of the most frequent users of UFH in Japan. However, none of our patients was diagnosed with HIT before 2001, when a sentinel event provoked the attention of our staff, as described later.

An 81-year-old woman with atrial fibrillation was admitted for cardioembolic stroke of the right middle cerebral artery. Intravenous UFH administration (10,000 U/day) was started 4 days after admission. Seven days after the start of UFH, her platelet count suddenly dropped from 175 to $37 \times 10^3/\mu L$ (Fig. 1). Two days later, she suffered from right lower limb arterial thrombosis, ultimately resulting in limb amputation, with hypercoagulable state, low fibrinogen: 1.3 g/L (reference interval, 1.5 to 3.4), elevated thrombin-antithrombin complex: >60 μg/L (reference interval, <2), and fibrin/fibrinogen degradation products: 109 μg/mL (reference interval, <5). Nevertheless, the administration of UFH continued for a total of 14 days because her physicians attributed these symptoms to DIC and did not consider HIT in the differential diagnosis. Finally UFH was stopped and replaced with argatroban, resulting in a rapid recovery of her platelet count. The diagnosis of HIT was supported by an enzyme-linked immunosorbent assay (ELISA) positive for antiplatelet factor 4/heparin antibodies (anti-PF4/heparin antibodies). We did not perform any functional assay for HIT. The recently developed 4 T's scoring system to determine the pretest probability of HIT,[9,13,23] if applied to this case, yields the top score of 8, indicating a very high probability of HIT.

Confronted with this shocking case of an anticoagulant turned procoagulant, we acknowledged the fundamental paradox of HIT and proceeded to investigate the clinical profile of HIT in Japan.

ARGATROBAN ANTICOAGULANT MANAGEMENT FOR CARDIOPULMONARY BYPASS IN PATIENTS WITH ACUTE HEPARIN-INDUCED THROMBOCYTOPENIA

Alternative anticoagulant therapy is strongly recommended for acute HIT cases[1,20,24,25] because HIT is associated with a high frequency of thrombosis despite discontinuation of heparin. The initial rate of thrombosis is ~6% per day over the first 1 to 2 days,[24] and the incidence of new thromboembolism falls as soon as an alternative anticoagulant is initiated.[26]

However, alternative anticoagulants, especially those that have no antidote and/or have a long half-life, can cause severe complications such as serious

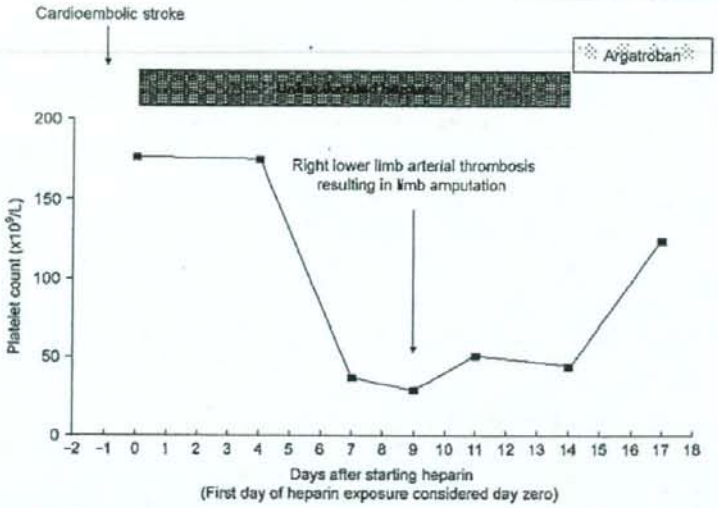

Figure 1 The first case diagnosed as heparin-induced thrombocytopenia (HIT) in our institute: An 81-year-old woman who was treated with unfractionated heparin (UFH) for cardioembolic stroke developed thrombocytopenia with hypercoagulable state 7 days after starting heparin. Her physicians initially made a diagnosis of disseminated intravascular coagulation and continued UFH administration, leading to arterial thrombosis of her right lower limb. Finally UHF was replaced with argatroban, resulting in a rapid recovery of her platelet count. The diagnosis of HIT was supported by the presence of antiplatelet factor 4/heparin antibodies.

bleeding[27–30] and adverse drug reactions,[31] especially in critically ill patients. Alternative anticoagulation for acute HIT is especially problematic in cases that require cardiovascular surgery with CPB[27] for which heparin is the only well-established anticoagulant. Trials using danaparoid, approved only for DIC in Japan, were reported for such cases. In some reports, this anticoagulant led to life-threatening bleeding[27,30] due to danaparoid's long plasma elimination half-life (20 hours) and lack of point-of-care testing for danaparoid such as the activated clotting time (ACT).

In contrast, argatroban may have an advantage because it has a much shorter plasma half-life (40 to 50 minutes) and it can be monitored by the ACT. On this basis, we considered argatroban as the alternative anticoagulant for patients with acute HIT who required surgery with CPB. Reports of anticoagulation with argatroban are sporadic[32–35] and variable with regard to dosing and management in this clinical indication. We describe our dosing and management techniques for CPB with argatroban as follows.

Cardiopulmonary Bypass Patients 1 and 2

A 47-year-old man was transferred to our hospital with dilated cardiomyopathy (DCM) requiring an intra-aortic balloon pump (IABP). Eight days after initiation of heparin therapy for IABP, he developed thrombocytopenia with arterial line occlusion. His platelet count normalized within 5 days of starting argatroban as an alternative anticoagulant (Fig. 2, left panel).

Shortly thereafter, another patient with DCM, a 23-year-old woman, was admitted for catheter ablation for ventricular tachycardia. Emergency surgery using CPB was performed for removal of the atrial thrombosis that was discovered during the procedure of catheter ablation. Heparin was continued thereafter. Her platelet count dropped to 67,000/μL 5 days after the initiation of postoperative heparin therapy. Her platelet count also recovered soon after the administration of argatroban (Fig. 2, right panel).

The diagnosis of HIT was supported in both cases by the detection of plasma anti-PF4/heparin antibodies by ELISA. Both patients ultimately had end-stage heart failure requiring the implantation of a left ventricular assist device (LVAD) bridging to heart transplantation. After approval from the ethics committee with their informed consent, their LVAD implantations were performed using argatroban as an anticoagulant for CPB. Standard anesthetic and surgical techniques were performed except for anticoagulant management for CPB. Non-heparin-bonded circuits were used.

In both cases, argatroban was administrated via a central venous line at a dose of 0.1 to 0.3 mg/kg followed by a continuous infusion at 5 to 25 μg/kg/minute to achieve a target ACT of $\geq$480 seconds before the commencement of CPB (Figs. 3A and 4A). Additionally, 0.05 mg/kg of argatroban was added to the CPB apparatus priming solutions. During CPB, argatroban

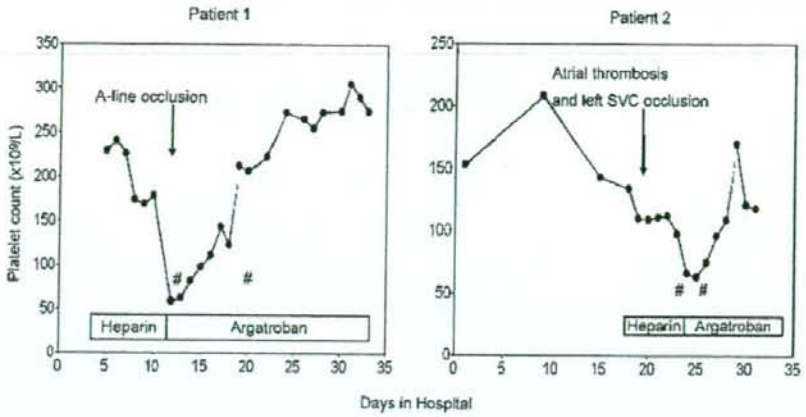

Figure 2 Clinical course in two patients with dilated cardiomyopathy leading to the diagnosis of heparin-induced thrombocytopenia. Patient 1, a 47-year-old man, developed thrombocytopenia with arterial line occlusion 8 days after initiation of unfractionated heparin (UFH) therapy for an intra-aortic balloon pump (left panel). Patient 2, a 23-year-old woman, underwent emergency surgery for the removal of an atrial thrombosis. She received postoperative thromboprophylaxis with UFH and developed thrombocytopenia 5 days after the initiation of thromboprophylaxis (right panel). Their platelet counts recovered soon after the administration of argatroban. #, Positive anti-PF4/heparin antibodies detected by an enzyme-linked immunosorbent assay; SVC, superior vena cava.

was also delivered through the sampling line into a venous reservoir and via a stopcock prior to the oxygenator to ensure a target ACT value >480 seconds. The ACT was monitored periodically and an additional 0.05 to 0.3 mg/kg of argatroban was administered or the continuous infusion rate of argatroban was adjusted as needed. To prevent blood clot formation, the retention time of blood in the surgical field was minimized. Argatroban was stopped at the termination of CPB.

The ACT during CPB ranged from 544 to >999 seconds (Figs. 3B and 4B). The ACT had returned to the control level in 12 or 7 hours after CPB, respectively (Figs. 3C and 4C). Continuous argatroban therapy was restarted for LVAD anticoagulation on the first postoperative day (POD). Total postoperative bleeding was 975 and 1197 mL, respectively. The postoperative course was uneventful in both patients.

The concentration of argatroban was measured by a liquid chromatography-electrospray tandem mass spectrometry. Good linear relationships between argatroban concentrations and ACT were observed before ($r=0.94$) and after ($r=0.90$) CPB (Fig. 5). However, no relationship was found during CPB ($r=0.81$; $p=0.192$) due to ACT values exceeding the detection limit (999 seconds) at argatroban concentrations >6.5 μg/mL and because few measurements ($n=4$) were made. The minimal argatroban concentration during CPB was 3.9 μg/mL, suggesting that the safe level of argatroban during CPB appears to be >3.9 μg/mL.

The regression line slope during and after CPB was unexpectedly steeper than that before CPB, indicating that argatroban had a much stronger anticoagulant effect on the ACT during and after CPB as compared with that before CPB, probably due to CPB-associated hemodilution, hypothermia, and consumptive coagulopathy. This may relate to the difficulty of ACT control during and after CPB, a cause of prolonged bleeding, which was also shown in another report.[35] No blood clot was observed either in the oxygenator or the arterial line filter in both cases, as examined by electron microscopy. This result, together with the fact that ACT values exceeded the detection limit at the end of CPB in both patients (Figs. 3B and 4B), suggests that the lower amount of argatroban at the end of CPB may be sufficient for the appropriate management of LVAD implantation during CPB than what was used in our two cases.

Both patients had successful heart transplants using UFH as an anticoagulant for CPB after their anti-PF4/heparin antibodies became negative.

Cardiopulmonary Bypass Patient 3

We encountered one fatality, suspected of having acute HIT, after open-heart surgery with CPB anticoagulated by argatroban. A 72-year-old man underwent aortic valve replacement with coronary artery bypass grafting with CPB anticoagulated by UFH. Immediately after surgery, he suffered from heart failure and renal dysfunction, requiring open chest interventions, catecholamine support including epinephrine infusion, and continuous hemodiafiltration (CHDF). Platelet counts from 30,000 to 60,000/μL persisted during CHDF, for which UFH was administered until POD 11, despite multiple platelet concentrate transfusions.

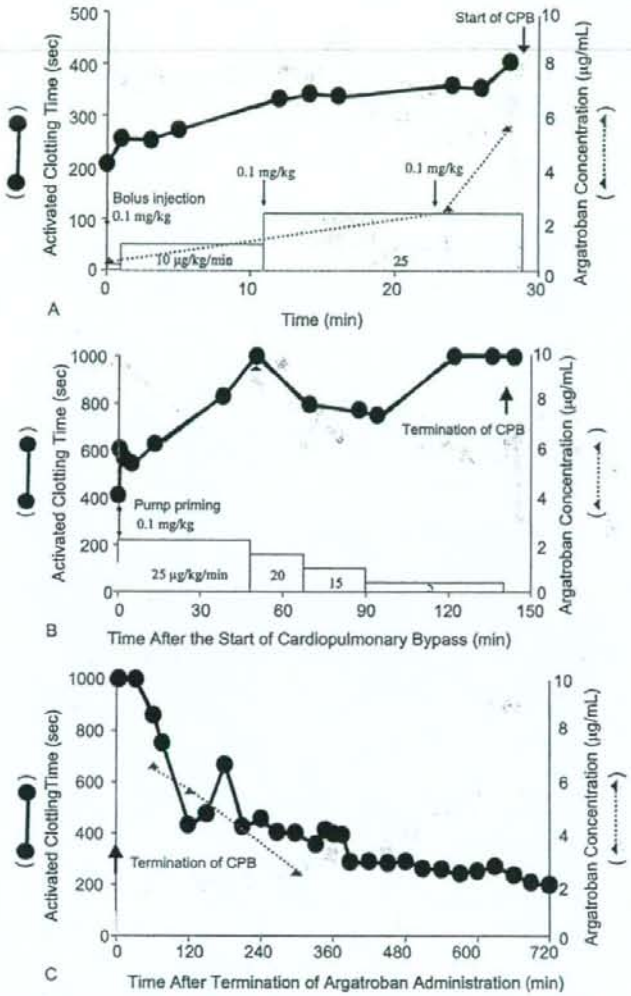

Figure 3 Serial changes in the dose of argatroban, activated clotting time (ACT), and plasma argatroban concentration (A) before, (B) during, and (C) after cardiopulmonary bypass (CPB) for the implantation of a left ventricular assisted device in Patient 1 with acute heparin-induced thrombocytopenia (see details in Fig. 2). (A) Argatroban was administrated at a dose of 0.1/kg followed by a continuous infusion at 5 to 25 μg/kg/minute to achieve a target ACT of ≥480 seconds before the commencement of CPB. (B) The ACT was monitored periodically and an additional 0.1 mg/kg of argatroban was administered for pump priming. The continuous infusion rate of argatroban was gradually reduced, monitoring ACT to maintain ≥480 seconds, and argatroban was stopped at the termination of CPB. (C) The ACT returned to the control level 12 hours after CPB.

Within 2 days after discontinuing CHDF and UFH, his platelet count increased to ~90,000/μL. The result of ELISA showed positive anti-PF4/heparin antibodies on POD 11.

Soon after this event, the patient required an urgent reoperation for re-aortic valve replacement with CPB due to severe perivalvular aortic regurgitation. The evolution of his platelet count following the first surgery was atypical. The common biphasic pattern,[17] in which CPB-induced thrombocytopenia recovers before HIT evolves, was not observed in this patient, and because CHDF itself can provoke a continuously low platelet count, a diagnosis of HIT was not obvious. However, the relatively high level of anti-PF4/heparin antibodies (>1.0 optical density)[36] persuaded us to use argatroban as an anticoagulant for CPB.

Following argatroban as an anticoagulant during CPB, plasma exchange after CPB was used in an attempt to remove argatroban from the blood, but this procedure was abandoned because of circulatory instability.

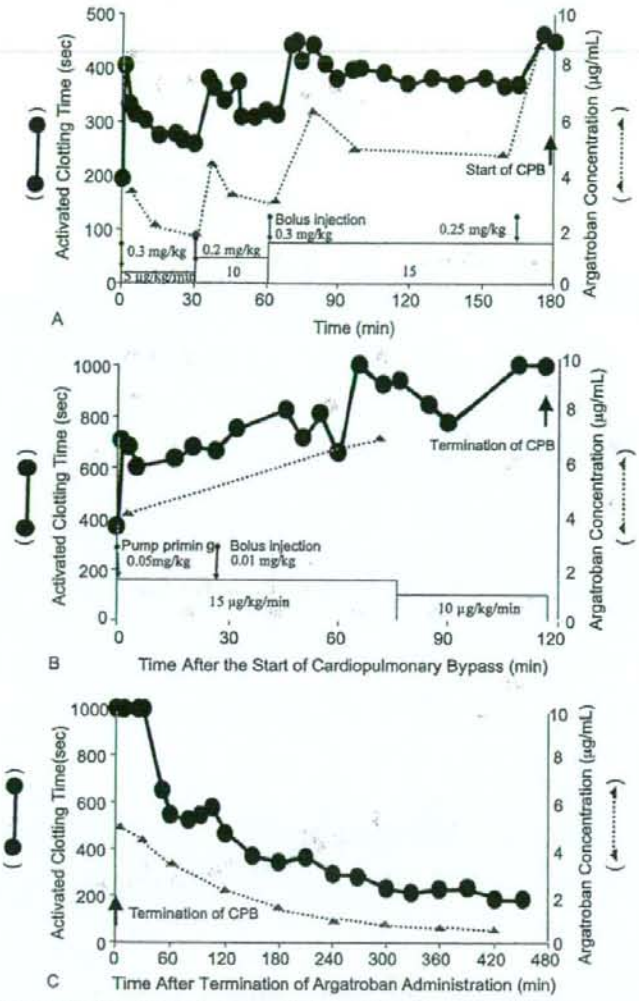

Figure 4 Serial changes in the dose of argatroban, activated clotting time (ACT), and plasma argatroban concentration (A) before, (B) during, and (C) after cardiopulmonary bypass (CPB) for the implantation of a left ventricular assisted device in Patient 2 with acute heparin-induced thrombocytopenia (see details in Fig. 2). (A) The same strategy was used as described in Figure 3 with minor modifications: increased dose of bolus injections (0.2 to 0.3 mg/kg) and reduced continuous dose (5 to 15 μg/kg/minute) before the commencement of CPB attempting to avoid overshooting of ACT. (B) But the ACT reached > 999 at the end of surgery. (C) The ACT returned to the control level 7 hours after CPB.

Unfortunately, the patient died of myocardial dysfunction, sustained ventricular tachycardia/ventricular fibrillation, and bleeding including focal subarachnoid hemorrhage 1 day after the reoperation. In this case, the control of ACT was much more difficult as compared with the two cases described earlier because the patient required repeated CPB management and percutaneous cardiopulmonary support after CPB.

Through these events, we recognize that the use of argatroban during CPB is promising, but further modifications of technique, especially anticoagulation monitoring, should evolve. Bivalirudin has shown promise as an anticoagulant for CPB in patients with acute HIT, and the strategy of bivalirudin anticoagulation for CPB has been reported.[37–41] However, bivalirudin is not available in Japan. We now recommend that cardiovascular surgery requiring systemic anticoagulation with or without CPB for acute HIT patients should be postponed as long as possible until the patient's anti-PF4/heparin antibody level becomes negative.[10,42,43] In addition, a careful diagnostic workup for HIT, as described later, should be followed.

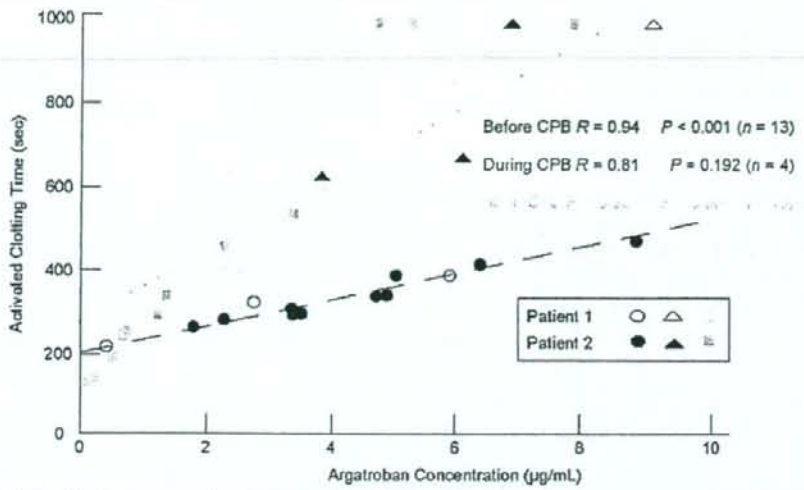

Figure 5 Relationship between activated clotting time (ACT) and plasma argatroban concentration. Plasma argatroban concentrations were assessed by a liquid chromatography-electrospray tandem mass spectrometry periodically throughout the surgeries of Patient 1 (open marks) and Patient 2 (closed marks) (see details in Figs. 3 and 4). Good linear relationships between plasma argatroban concentrations and ACT were observed before ($r = 0.94$, $p < 0.001$; ○ and ●) and after ($r = 0.90$, $p < 0.001$; □ and ■) cardiopulmonary bypass (CPB). No relationship was found during CPB ($r = 0.81$, $p = 0.192$; Δ and ▲) due to ACT values exceeding the detection limit (999 seconds) at argatroban concentrations > 6.5 μg/mL and few measurements ($n = 4$). Note that the slope of the regression line during and after CPB was steeper than that before CPB.

INCIDENCE OF HEPARIN-INDUCED THROMBOCYTOPENIA IN THE JAPANESE POPULATION

HIT is a clinicopathological syndrome. Thus the definitions of both clinical diagnosis and serological tests are very important and may profoundly influence the reported incidence of HIT.[12,14,36,44] ELISA for detecting anti-PF4/heparin antibodies is now popular in Japan, but no functional assay using washed platelets has been established with high quality control. Thus we must diagnose HIT through a combination of clinical pretest probability (e.g., the 4 T's scoring system) and ELISA results. Overdiagnosis arising from the low specificity of this approach is a distinct possibly.[14,44]

Previous reports in Western countries have indicated that the incidence of HIT is ~1 to 3% in cardiac surgery patients where UFH is used for routine postoperative prophylaxis.[14,17,45,46] But routine heparin prophylaxis is not common in Japan in this patient population. However, acute ischemic stroke patients frequently receive UFH therapy, despite the lack of supporting evidence. We have conducted retrospective studies at our institute and a multicenter, prospective cohort study to determine the incidence of HIT in these clinical settings.

Among cardiovascular surgery or acute ischemic stroke patients who were treated with UFH, we have retrospectively investigated those who were clinically suspected of having HIT during the last several years. A commercially available ELISA (Asserachrom HPIA; Diagnostica Stago; Asnières, France) assay was used to screen HIT patients. Clinically suspected HIT patients were evaluated by ^{14}C-serotonin release assay (SRA), kindly performed by Prof. Walenga and her colleagues at Loyola University Medical Center (Maywood, IL), to confirm the HIT diagnosis.

We have also conducted a multicenter, prospective cohort study to determine the incidence and profile of HIT in patients undergoing cardiovascular surgery or PCI.[21] Patients scheduled to undergo cardiovascular surgery ($n = 1,444$) or PCI ($n = 110$) were enrolled between November 2004 and December 2005 at 11 institutions. We followed the patients for 30 days after surgery or PCI and examined the patients' history, demographic data, changes in platelet count, and timing and period of heparin administration including heparin flush, complications, thromboembolism, and death. We took blood samples before, 7 days after, and 14 days after the surgery or PCI to test for HIT antibodies. The diagnosis of HIT was confirmed by SRA, kindly performed by Prof. Warkentin and his colleagues at the Coagulation Laboratory, McMaster University (Hamilton, ON, Canada).

Because the reports of these studies are not yet published, we cannot cite them in detail. However, our preliminary data suggest that the incidence of HIT in the Japanese population appears to be lower (e.g., by about one order of magnitude in patients undergoing

cardiovascular surgery) than those reported in Western countries. Ethnic factors and/or different clinical practices (e.g., routine heparin prophylaxis after the surgery is not common in Japan) may contribute to the low apparent incidence of HIT in the Japanese population.

CLINICAL TRIAL ON THE EFFICACY AND SAFETY OF ARGATROBAN IN JAPANESE PATIENTS WITH HEPARIN-INDUCED THROMBOCYTOPENIA

To overcome our problem that no drug for HIT treatment has been approved by Japanese regulators, we have conducted a multicenter, nonrandomized, open-label trial at 20 institutions to evaluate the efficacy and safety of argatroban in patients with HIT.[22] The same protocol as used in ARG-911[47] with minor modifications was followed; in particular, a reduced initial dosage of argatroban was used.

In our institution, we had used the same initial dose (2 μg/kg/minute in patients with normal liver function and 0.5 μg/kg/minute in those with hepatic impairment) as recommended in the United States by manufacturers' prescribing information. With this dosing regimen, we encountered serious bleeding with rapid increase of activated partial thromboplastin time (aPTT)

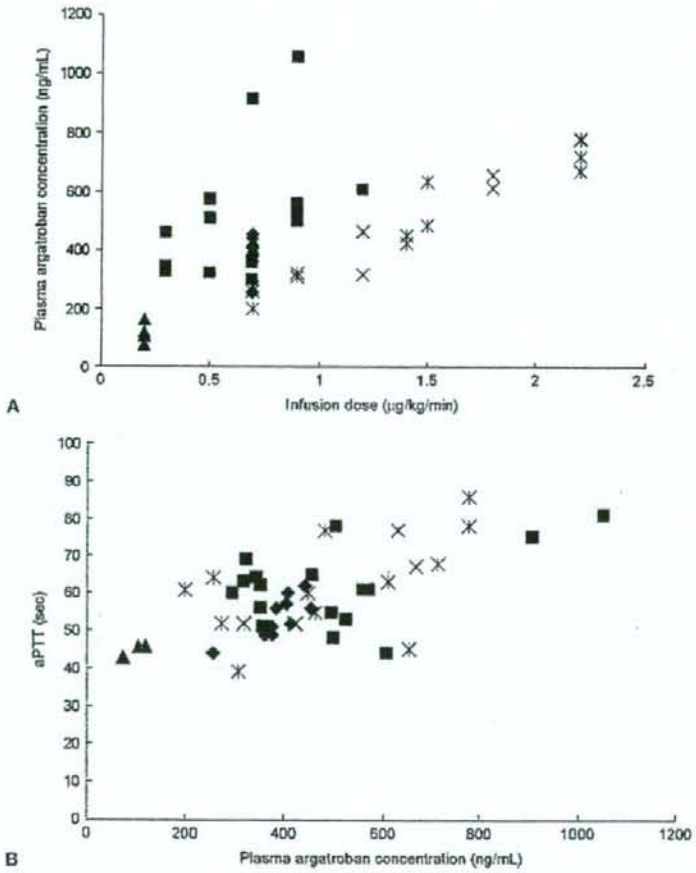

Figure 6 Relationships of argatroban dose or activated partial thromboplastin time (aPTT) versus plasma argatroban concentration. Plasma argatroban concentrations were examined in four patients as a substudy in the multicenter, nonrandomized, open-label trial to evaluate the efficacy and safety of argatroban in patients with heparin-induced thrombocytopenia. The initial dosages of argatroban were 0.7 μg/kg/minute in three patients (■, ◆, •) with normal liver function and 0.2 μg/kg/minute in one patient (▲) with a risk factor for bleeding, respectively. These doses are about a third the initial dose recommended by the manufacturer in the United States and Europe. (A) However, almost all infusion doses (even < 1 μg/kg/minute) increased the plasma argatroban concentration to > 200 ng/mL, sufficient to keep the aPTT within the target range (B), except in one patient (▲) whose argatroban therapy was terminated due to intracranial hemorrhage before his aPTT prolonged to the target range. (B) Plasma argatroban concentrations showed a good correlation with the values of aPTT (r = 0.62).

beyond the target range in several postcardiovascular surgery patients.[29] Moreover, several reports from the United States[28] and Germany[48,49] have suggested that a lower starting dose of argatroban may be sufficient and safe for effective anticoagulation, especially in critically ill patients.

Thus, in our protocol, initial dosing of argatroban was reduced to 0.7 μg/kg/minute in patients with normal liver function and 0.2 μg/kg/minute in those with hepatic impairment or a risk factor for bleeding. This was about a third the initial dose recommended by the manufacturer in the United States and Europe. However, the aPTT was targeted in the same range (1.5 to 3 times baseline aPTT). For patients with a risk factor for bleeding, 1.5 to 2 times baseline aPTT was recommended.

Thereafter, 8 patients were enrolled between July 2005 and September 2006. Among them, two patients who had a documented history of positive anti-PF4/heparin antibodies and required anticoagulation therapy were enrolled even in the absence of thrombocytopenia (defined as a platelet count $< 100{,}000/\mu L$ or $> 50\%$ reduction in count after heparin therapy with no explanation other than HIT) at enrollment.

The total number of enrolled patients was much smaller than expected, consistent with the results of other clinical research showing a low incidence of HIT in Japan as described earlier. Argatroban was initiated at a dose of 0.7 μg/kg/minute in 5 patients and 0.2 μg/kg/minute in 3 patients. Even using these lower initial doses, the aPTT was prolonged to the target range (1.5 to 3 times baseline aPTT value) within ~2 hours of initiation of infusion in 6 patients (75%). The primary endpoint (composite of death, amputation of extremities, and new thrombosis) occurred in one patient (posterior tibial artery thrombosis). Thrombocytopenia was resolved in 33% of patients within 3 days after starting argatroban treatment and in 83% of patients during treatment. Two patients who had a documented history of positive HIT antibodies in the absence of thrombocytopenia at enrollment were excluded from the analysis of thrombocytopenia resolution.

One major hemorrhagic event (intracranial hemorrhage) with symptomatic epilepsy without neurological deficit occurred in the patient with a platelet count of $3{,}000/\mu L$ 2 days after starting therapy. The administration of argatroban was promptly terminated in this patient. Minor hemorrhagic events occurred in two patients.

Concomitant with this clinical trial, plasma argatroban concentrations were examined in four patients as a substudy. Almost all infusion doses (even < 1 μg/kg/minute) increased the plasma argatroban concentration properly (Fig. 6A), sufficient to maintain the aPTT within the target range (Fig. 6B). The exception was one patient who had an intracranial hemorrhage as described earlier and whose argatroban therapy was terminated before his aPTT prolonged to the target range. Plasma argatroban concentrations showed a good correlation with the values of the aPTT ($r = 0.62$), as shown in Fig. 6B.

The results of our clinical trial appear to be compatible with those of the ARG-911 trial,[47] although the total number of enrolled patients in our trial is too small for statistical analysis. Argatroban seems to be effective and safe for the treatment of HIT but requires careful consideration of the initial dosage. Based on the results of our trial, two pharmaceutical companies are now submitting an application to the Japanese regulators for approval of argatroban to treat patients with HIT.

CONCLUSIONS

Immune-mediated heparin-induced thrombocytopenia is a life-threatening side effect of heparin therapy. Although it appears that the incidence of HIT is lower in Japan than in Western counties, the serious morbidity and mortality profile of HIT warrants our continued attention. In acute HIT, cardiovascular surgery using CPB should be postponed as long as possible until the patient's anti-PF4/heparin antibody test becomes negative and UHF can be used as the CPB anticoagulant. For acute HIT patients who require immediate surgery with CPB, the risk/benefit profile of argatroban anticoagulation should be carefully considered. Argatroban appears to be effective and safe for treatment of Japanese HIT patients when properly dosed. Our dosing schedule is safe and effective at lower doses than those recommended elsewhere. These results should be considered in other demographic settings.

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DISCLOSURES

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Hemostatic Management During Oral Surgery in Patients With a Left-Ventricular Assist System Undergoing High-Level Anticoagulant Therapy: Efficacy of Low Molecular Weight Heparin

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Mechanical circulatory support (MCS), such as the left-ventricular support system (LVAS), is a useful therapeutic option as a bridge to recovery or to heart transplantation in patients with severe cardiac failure. Thromboembolism, infection, and bleeding represent the major managerial problems in patients receiving MCS. Because clots are likely to form during MCS, high-level anticoagulant therapy (prothrombin time-international normalized ratio [PT-INR] ≥3.0 to 4.0) is a required aspect of patient management.[1] In candidates for heart transplantation, oral infections must be completely eliminated, which often necessitates oral surgery; however, hemostatic management is difficult in such patients, who typically receive high-level anticoagulant therapy.

At present, when performing tooth extraction in a patient receiving antithrombotic therapy, administration of antiplatelet agents is continued, and surgery is generally performed with the patient receiving warfarin as long as the patient's PT-INR remains ≤3.5.[2] However, in MCS patients on high-level anticoagulant therapy (PT-INR ≥3.0 to 4.0), intraoperative hemo-

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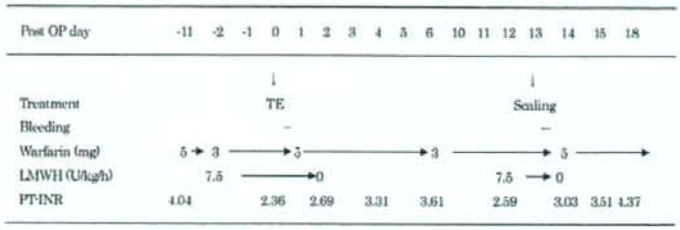

FIGURE 1. Case 1. Tooth extraction was performed with the patient at PT-INR 2.36 and receiving continuous IV administration of dalteparin 7.5 U/kg/h.

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LMWH: low-molecular-weight heparin (Dalteparin), PT-INR: prothrombin time-international normalized ratio
TE: tooth extraction

static management according to conventional therapeutic approaches is difficult.

We performed oral surgery on a group of patients on LVAS, who were receiving continuous intravenous (IV) administration of low molecular weight heparin (LMWH). Good hemostatic management was achieved in all patients.

Report of Cases

Our subjects are 4 patients who were being managed by LVAS (Toyobo Co, Osaka, Japan) at the National Cardiovascular Center. All 4 patients received antiplatelet and high-level anticoagulant therapy (PT-INR ≥ 3.0 to 4.0) and underwent oral surgery while receiving continuous IV administration of LMWH (dalteparin). No thrombus formation in the LVAS was observed during the procedure in any of the patients. All patients received antibiotics before and after surgery for infection prophylaxis.

CASE 1

In this 48-year-old woman with dilated hypertrophic cardiomyopathy, tooth extraction was planned due to marginal periodontitis at the mandibular left first premolar. Her antithrombotic therapy comprised aspirin 162 mg/day and warfarin 4 to 5 mg/day. At 1 month before surgery, her PT-INR ranged from 3.26 to 4.37. Starting 2 days before tooth extraction, her warfarin dose was reduced from 5.0 to 3.0 mg/day and continuous IV administration of dalteparin 7.5 U/kg/h was initiated. Tooth extraction was performed with the patient at PT-INR 2.36, and the gingiva was sutured after placement of oxidized cellulose cotton. No postoperative bleeding occurred. The warfarin dose was increased to 5.0 mg/day starting on the day after surgery, and dalteparin was discontinued with the patient at PT-INR 2.69 on day 2 after surgery (Fig 1).

CASE 2

In this 42-year-old woman with dilated cardiomyopathy, 3 tooth extractions were planned due to apical periodontitis at the maxillary right second premolar and both left and right lateral incisors and canines, and the mandibular left first and second premolars and right second molar. As antithrombotic therapy, she received 81 mg/day of aspirin and 3 to 5 mg/day of warfarin. Her PT-INR during the month before surgery ranged from 3.57 to 4.47. Starting 2 days before the first tooth extraction, her warfarin dose was reduced from 3.0 to 1.5 mg/day, and continuous IV administration of 7.5 U/kg/h of dalteparin was initiated at the same time. In the first operation, 3 teeth were extracted with the patient at PT-INR 1.25, and local hemostasis was achieved in the same manner as in case 1. No postoperative bleeding occurred; however, the patient complained of headaches starting on day 2 after surgery. Although a brain computed tomography scan showed no hemorrhage, dalteparin was discontinued due to the possibility of brain hemorrhage. The patient's headaches improved with 2 days of rest, and no neurologic sequelae were seen. The subse-

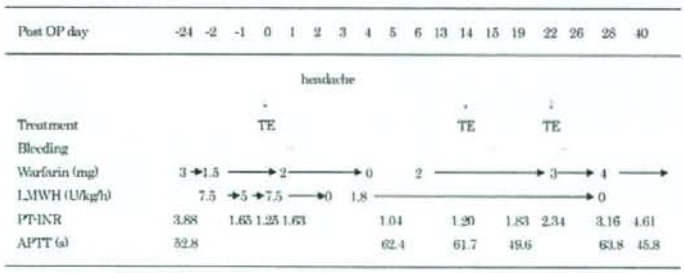

FIGURE 2. Case 2. Tooth extractions were performed with the patient at PT-INR 1.20 to 2.34 and receiving continuous IV administration of dalteparin 7.5 or 1.8 U/kg/h.

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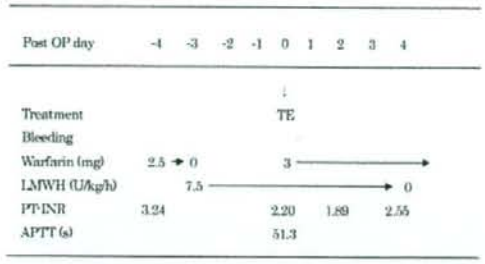
APTT normal range: 24 ~ 40 s
LMWH: low-molecular-weight heparin (Dalteparin), PT-INR: prothrombin time-international normalized ratio,
APTT: activated partial thromboplastin time, TE: tooth extraction



APTT normal range: 24~40s
LMWH: low-molecular-weight heparin (Dalteparin),
PT-INR: PT: prothrombin time-international normalized ratio
APTT: activated partial thromboplastin time, TE: tooth extraction

FIGURE 3. Case 3. Tooth extraction was performed with the patient at PT-INR 2.20 and receiving continuous IV administration of dalteparin 7.5 U/kg/h.

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quent 2 tooth extraction surgeries were performed uneventfully using warfarin 2.0 mg/day and dalteparin 1.8 U/kg/h with the patient at PT-INR 1.20 and 2.34, respectively. No postoperative bleeding occurred (Fig 2).

CASE 3

In this 48-year-old man with dilated cardiomyopathy, tooth extraction was planned due to marginal periodontitis at the mandibular left first molar. As antithrombotic therapy, the patient was receiving aspirin 162 mg/day and warafarin 2.5 to 5.0 mg/day. His PT-INR during the month before surgery ranged from 3.24 to 4.82. Three days before tooth extraction, warfarin was discontinued and continuous IV administration of dalteparin 7.5 U/kg/h was initiated. Tooth extraction was performed with the patient at PT-INR 2.20, and hemostasis was achieved in the same manner as in case 1. No postoperative bleeding occurred. Warfarin administration was resumed on the day after surgery at 3.0 mg/day, and dalteparin was discontinued on day 4 after surgery with the patient at PT-INR 2.55 (Fig 3).

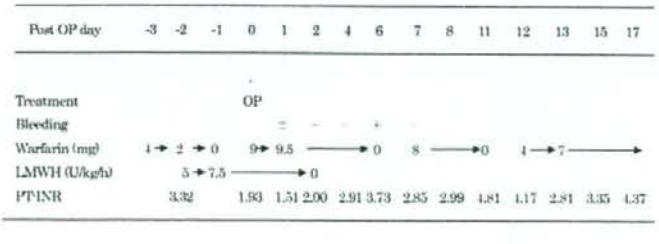
CASE 4

In this 17-year-old woman with dilated cardiomyopathy, cystectomy and apicoectomy were planned due to radicular cysts at the maxillary left central and lateral incisors. As antithrombotic therapy, she was receiving aspirin 81 mg/day and warfarin 4 to 5 mg/day. Her PT-INR during the month before surgery ranged from 3.32 to 5.14. Starting 2 days before tooth extraction, her warfarin dose was reduced to 2.0 mg/day and then discontinued, and continuous IV administration of dalteparin 7.5 U/kg/h was initiated. Cystectomy and apicoectomy with concomitant gingival incision and removal of bone were performed with the patient at PT-INR 1.93, and the gingiva was sutured after hemostasis was achieved using bone wax and oxidized cellulose cotton. No postoperative bleeding occurred. Warfarin administration at 9.0 mg/day was resumed on the night of surgery, and dalteparin was discontinued with the patient at PT-INR 2.0 on day 2 after surgery. However, intermittent oozing was confirmed from the gingival margin 6 days after surgery. At this point, the patient's PT-INR was high (3.73). Hemostasis was achieved by compression and discontination of warfarin with the patient at PT-INR 2.85 (Fig 4).

Discussion

Regarding oral surgery for patients on MCS, during surgery, Lund et al[1] continued to administer an antiplatelet agent and switched from warfarin to IV unfractionated heparin. In that study, 4 of 6 patients experienced complications: 2 patients displayed wound bleeding, 1 patient developed thrombosis, and 1 experienced both. Lund et al concluded that oral surgery should not be performed on patients receiving MCS.[1] However, here we report the safe performance of oral surgery on 4 patients being managed with LVAS and receiving antiplatelet agents and high-level anticoagulant therapy (PT-INR around 4.0) by reduction or termination of warfarin and continuous administration of IV LMWH (dalteparin) 7.5 U/kg/h to lower the PT-INR to 1.20 to 2.36.

Whereas conventional unfractionated heparin suppresses both factor X and thrombin, dalteparin selectively suppresses factor X. Although dalteparin exhibits anticoagulation activity, it does not suppress thrombin, so activated partial thromboplastin time (APTT) is not markedly increased and bleeding is less likely to occur.[3,4] In Japan, the use of dalteprin 7.5 to



LMWH: low-molecular-weight heparin (Dalteparin), PT-INR: prothrombin time-internat ional normalized ratio,
APTT: activated partial thromboplastin time, OP: operation

FIGURE 4. Case 4. The operation was performed with the patient at PT-INR 1.93 and receiving continuous IV administration of dalteparin 7.5 U/kg/h. Postoperative hemorrhage was observed 6 days after surgery.

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10 U/kg/h is approved for anticoagulant therapy during extracorporeal circulation.[5] In the present series of patients, as a general rule, dalteprin 7.5 U/kg/h was continuously administered IV without increasing APTT or causing thrombus formation in the LVAS.

Todd et al[6] and Leong et al[7] reported extracting teeth without inducing thrombosis or bleeding by terminating warfarin and subcutaneously administering 30 to 40 mg/day of LMWH (enoxaparin); however, Bloomer[8] reported postoperative bleeding using the same approach. Kovacs et al[9] performed surgery on 224 patients on antithrombotic therapy (including 25 patients who underwent tooth extraction) by discontinuing warfarin and administering dalteparin subcutaneously. In that study, warfarin was discontinued 5 days before surgery, dalteprin 200 U/kg/day was administered subcutaneously on 2 and 3 days before surgery, dalteprin 100 U/kg/day was administered subcutaneously on the day before surgery, and no dalteparin was administered on the day of surgery. Surgery was performed with the patient at PT-INR <1.5. The frequencies of thrombosis and severe bleeding were 3.6% and 6.7%, respectively; 1 of the 25 patients who underwent tooth extraction experienced thrombosis. Douketis et al[10] performed surgery on 650 patients receiving antithrombotic therapy using almost the same dalteparin regimen as described by Kovacs et al.[9] In 542 of the 650 patients who underwent a non-high-bleeding risk procedure, the frequency of thrombosis was 0.4%, that of severe bleeding was 0.7%, and that of wound bleeding was 5.9%.[10]

In the present study, all 4 patients received continuous IV administration of dalteparin 7.5 U/kg/h. This is equivalent to a dose of 180 U/kg/day, comparable to the dose used by Kovacs et al[9] and Douketis et al.[10] Warfarin can be decreased to below the hemostatic level in oral surgery (PT-INR < 3.5) when dalteparin is administered continuously. Favorable hemostasis was achieved in our 3 patients who underwent tooth extraction by placing oxidized cellulose cotton and suturing.

In the patient who underwent jawbone surgery, favorable hemostasis was achieved during dalteparin administration, but bleeding occurred on day 6 postoperatively after making the switch from dalteparin to warfarin, with the patient at PT-INR 3.73. When compression cannot be applied directly in this type of wound, careful intraoperative hemostatic management and wound observation are necessary. If hemostasis proves difficult, then a reduction of warfarin dose must be considered.

Although several studies have explored the optimal administration route and dosage of LMWH,[3,9-12] dosage guidelines for various scenarios have not yet been set, and further investigation is needed. Whereas the standard IV dose of dalteparin is 7.5 to 10 U/kg/h, dalteparin does not affect laboratory tests such as APTT. With the Toyobo LVAS, thrombosis can be macroscopically observed inside the blood pump; however, careful monitoring of clinical symptoms is necessary due to the risk of severe bleeding, such as intracranial hemorrhage.

In summary, our findings suggest that when performing oral surgery on LVAS patients undergoing high-level anticoagulant therapy (with PT-INR ≥ 3.0 to 4.0), hemostasis can be favorably managed by reduction or discontinuation of warfarin and continuous IV administration of dalteparin 7.5 U/kg/h.

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