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Review Article

Expert consensus for the treatment of disseminated intravascular coagulation in Japan

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ABSTRACT

The present report from The Japanese Society of Thrombosis and Hemostasis provides an expert consensus for the treatment of disseminated intravascular coagulation (DIC) in Japan. Disseminated intravascular coagulation (DIC) may be classified as follows: asymptomatic type, marked bleeding type, and organ failure type. Although treatment of DIC is important, adequate treatment differs according to type of DIC. In asymptomatic DIC, low molecular weight heparin (LMWH), synthetic protease inhibitor (SPI), and antithrombin (AT) are recommended, although these drugs have not yet been proved to have a high degree of effectiveness. Unfractionated heparin (UFH) and danaparoid sodium (DS) are sometimes administrated in this type, but their usefulness is not clear. In the marked bleeding type, LMWH, SPI, and AT are recommended although these drugs do not have high quality of evidence. LMWH, UFH, and DS are not recommended in case of life threatening bleeding. In case of severe bleeding, SPI is recommended since it does not cause a worsening of bleeding. Blood transfusions, such as fresh frozen plasma and platelet concentrate, are also required in cases of life threatening bleeding. In the organ failure type, including sepsis, AT has been recommended based on the findings of several clinical trials. DIC is frequently associated with thrombosis and may thus require strong anticoagulant therapy, such as LMWH, UFH, and DS.

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Introduction

Disseminated intravascular coagulation (DIC) is generally considered to be characterized by intravascular activation of coagulation with the loss of localization, which mainly occurs in the small veins and arteries due to various causes. The most common underlying diseases in patients with DIC are leukemia, infectious diseases, solid cancer, obstetric complications and aortic aneurysms [1]. The definition, concept, and diagnostic criteria of DIC were proposed by the Scientific Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) in 2001 [2].

Randomized clinical trials (RCT) of physiological protease inhibitors that limit activation of coagulation, such as antithrombin (AT)[3], activated protein C (APC)[4], and tissue factor pathway inhibitor (TFPI) [5], were recently carried out in patients with severe sepsis. As most patients with severe sepsis develop DIC, it would be expected that such protease inhibitors would contribute to an improved outcome. In the placebo groups of the KyberSept trial [3] (investigating the effect of AT) and the Prowess trial [6] (investigating the effect APC) the mortality rates measured on the 28th day was significantly higher in patients with DIC (40.0% and 43.0%, respectively) than in those without DIC (22.2% and 27.0%, respectively), thus suggesting that DIC is associated with a worse outcome in such patients. Other treatment modalities for DIC have have not yet been properly evaluated in RCTs.

So far, there is no universal consensus on the treatment of DIC. Less than half of all DIC are caused by sepsis, and existing reviews including guidelines on treatment of DIC concern only septic DIC in Europe and North America [7]. These reviews are based on RCTs in sepsis and not on DIC as a primary outcome. Guidelines on treatment of DIC are therefore almost all based on a subgroup analysis of patients with DIC. Our manuscript is therefore a useful supplement to the previously descrived approach of Europe and America.

The Japanese Society of Thrombosis and Hemostasis (JSTH) has established an expert consensus for DIC treatment based on the evidence as it applies to the clinicians giving medical care for primary DIC or underlying DIC [8]. It is anticipated these guidelines will help patients and their families to better understand DIC and to aid in the choice and execution of suitable medical treatment with mutual consent among medical workers and patients and their families.

This expert consensus is based on clinical evidence, but the evidence is at present limited. Therefore, the consensus is to a large degree based on frequent internal discussions including meetings to establish the level of recommendation for treatment of DIC. This expert consensus suggests standard treatment for DIC, but does not force the actual medical care action. The physician should decide on the appropriate treatment according not only on this expert consensus, but also based on the condition of individual patients and also on the institute where treatment will be given. This expert consensus has been approved by the inside evaluation committee of JSTH and outside evaluation committees of the Japanese Association for Acute Medicine (JAAM), the Japanese Society of Intensive Care Medicine, and The Japanese Association for Infectious Diseases.

Methods

JSTH established a committee to develop guidelines for treatment of DIC with the following members: Hideo Wada, Hidesaku Asakura, Kohji Okamoto, Toshiaki Iba, Toshimasa Uchiyama, Yutaka Eguchi, Kazuo Kawasugi, Shin Koga, Toshihiko Mayumi, Kaoru Koike, Satoshi Gando, Seiji Madoiwa, Shinji Ogura, Kenji Okajima, Mitsuhiro Uchiba, Naruki Kushimoto, Yoshinobu Seki and Youichi Sakata. On the basis of the concept for evidence based medicine (EBM), the committee systematically searched and reviewed the literature for DIC treatment, and the evidence level was determined based on a consensus of the findings in the literature with high levels of evidence. The recommendation level was determined according to the evidence level.

In treatment without a high level of evidence, the recommendation level of DIC treatment was determined by the consensus of all members based on the suggestions and comments from many experts at related conferences, forums, etc. The literature regarding meta-analyses, systematic reviews, or RCTs in DIC treatment were searched in both MEDLINE (Ovid) and Japana Centra Revuo Medicina by the key-words “disseminated intravascular coagulation” or “DIC”. The quality of evidence in each article was then determined according to the “Oxford centre for evidence-based medicine levels of evidence”[9]. The recommendation level was mainly decided according to the quality of evidence, but it was determined by consensus obtained at conferences and forums (Table 1)[10].

Results

I. Diagnosis of DIC

Up to now, three diagnostic criteria for DIC have been established: the DIC diagnostic criteria established by the Japanese Ministry of Health and Welfare (JMHW)[11], the ISTH (overt-DIC diagnostic criteria)[2], and the JAAM[12]. The DIC diagnostic criteria based on general coagulation tests, prothrombin time (PT), fibrinogen, FDP, and platelet count are similar. However, the criteria established by the JAAM are the most sensitive for septic DIC [13], the criteria by ISTH are the most specific for septic DIC, and the criteria established by JMHW are considered to be the most useful for the diagnosis of DIC in acute leukemia [14]. As the mortality rate of DIC is still high, early diagnosis and treatment are required.

Table 1
Recommendation levels (Modified Kish's Guide [7]).

Recommendation	
Consensus	Treatment does not have a high quality of evidence, but it should be carried out as common sense.
A	Treatment has high quality of evidence, and the clinical usefulness is clear.
B1	Treatment has moderately high quality of evidence, or it has high quality of evidence but the clinical usefulness is not significant.
B2	Treatment does not have a high quality of evidence, but it has few deleterious effects and it is carried out clinically.
C	Treatment does not have a high quality of evidence or the clinical usefulness is not clear.
D	Treatment has high quality of evidence, and it has deleterious effects.

These recommendation levels were determined according to “the guidelines of DIC treatment preparation committee” according to the evidence level and medical care of Japan. These expert consensus show the most standard treatment for DIC, but does not force the actual medical care actions. The Physician should decide on the adequate treatment according not only to these guidelines, but also according to the condition of each patient and institute.

II. Treatment of DIC

Level of recommendation: A *The treatment of DIC is considered to be essential (recommendation A), as follows.*

1. Treatment for underlying disease

Level of recommendation: consensus. 1019 articles in the literature relating to the treatment of underlying disease for DIC were obtained. There was no evidence concerning the prognosis of the underlying disease treatment by meta-analyses, systematic reviews, and RCTs, etc. It is common sense that administration an antibiotic specific for the infection is the most important therapy in septic DIC. After the administration of antibiotics, surgical drainage at the infection site is performed as soon as possible. Therefore, the doctor does first administer treatment for the underlying disease when sepsis is diagnosed. The treatment of the underlying disease is difficult to pursue with the purpose of establishing further evidence without having negative effects on the patients. Therefore, the treatment of the underlying disease was assumed to be agreed upon by consensus. Any infectious disease caused by any microorganism can trigger DIC, and DIC accompanied by sepsis is often experienced. The Surviving Sepsis Campaign [15] has recently been launched internationally for the treatment of sepsis. In RCTs, for all-transretinoic acid (ATRA) compared with conventional chemotherapy in acute promyelocytic leukemia (APL), the mortality of APL was significantly lower in the ATRA group ($n=176$) than in the conventional chemotherapy group ($n=174$) [16] (Level 1b). ATRA has not only a differential effect on APL but also anticoagulant and anti-fibrinolyitc effects.

2. Treatment with anticoagulant therapy

Level of recommendation: A Plasma derived APC [17] (Level 2b), recombinant thrombomodulin (rTM) [18] (Level 2b), rAPC [4](Level 1b), LMWH [19] (Level 2b) and ATRA [16] (Level 1b) are all considered to be effective treatments for sepsis or DIC. However, the drugs that have so far been approved by the Japanese Ministry Health and Welfare still lack sufficient evidence to prove their effectiveness. As ATRA reduces tissue factor (TF), anexin II, and plasminogen activator (PA) expression in APL cells [20] and various normal cells, ATRA decreases the frequency of early hemorrhagic death due to DIC and mortality.

1) Heparin/Heparinoid

Heparin/Heparinoid includes UFH, LMWH, and danaparoid sodium (DS). Though heparin or heparinoid does not itself have any anticoagulant activity, it increases the activity of AT to suppress thrombin activity and thus improves the hemostatic abnormalities of DIC. The side effects include hemorrhage and HIT. The administration of heparin is not recommended for life threatening bleeding, serious hepatic and renal failure which prolong the half-life. LMWH and DS both have relatively strong anti-Xa activity, but less anti-thrombin activity in comparison to UFH. A retrospective analysis [21] of each RCT of AT [3], APC [4], and TFPI [5] for severe sepsis showed that the mortality rate respectively tended to be lower in the low dose heparin group than in the placebo group. As this analysis was not a RCT for heparin use, physician bias may have favored the administration of heparin treatment.

a) UFH

Level of recommendation: C in general, B2 in thrombotic complication, D in severe hemorrhage. No systematic reviews, meta-analyses, or RCTs exist regarding the treatment of DIC with UFH. In the intensive care unit (ICU), most patients are treated with low dose heparin for the prevention of thromboembolism. In comparison with SPI and LMWH, no significant difference was observed in either survival rates or usefulness. In a comparison with plasma derived APC [17] and rTM [18], UFH was less effective than the control drugs. Even though there is still insufficient evidence for the use of UFH on DIC treatment, it is nevertheless considered to be the standard drug for DIC. Although UFH is recommended in patients associated with thrombosis, it is not used when remarkable hemorrhaging occurs.

b) LMWH

Level of recommendation: B2 in general, B1 in thrombotic complication, D in severe hemorrhage. Only dalteparin is approved for DIC treatment by Japanese Ministry Health and Welfare. In a multicenter co-operative double-blind trial [19] comparing dalteparin with UFH, dalteparin significantly reduced organ failure ($p<0.05$), reduced bleeding symptoms ($p<0.1$), and showed a higher safety rate than UFH ($p<0.05$, Level 2b). LMWH is therefore recommended for the treatment of DIC because the bleeding tendency was less than for UFH.

c) Danaparoid sodium (DS)

Level of recommendation: C, B2 in thrombotic complication,. DS is also approved for the treatment of DIC by the Japanese Ministry Health and Welfare. In a multicenter co-operative double-blind trial [22], no significant difference was observed in the efficacy and safety between DS and UFH (Level 2b). As DS does not completely counteract the anti-inflammatory action of AT [23], and the bleeding tendency after treatment with DS tends to be less than after UFH, DS is often used for thrombotic disease.

2) Synthetic or purified protease inhibitors (SPI)

Level of recommendation: B2 in general, B1 in hemorrhagic type SPIs include gabexate mesilate (GM), nafamstat mesilate (NM), and argatroban. GM and NM were initially approved for the treatment of pancreatitis and later were approved for the treatment of DIC by the Japanese Ministry Health and Welfare. GM [24,25] and NM [26] mildly inhibit the activity of thrombin, FXa, plasmin, and plasma kallikrein. As these do not cause bleeding, they are frequently used in patients with DIC in Japan [27]. While argatroban is a specific thrombin inhibitor and has strong anticoagulant activity, it also poses a high risk for bleeding. Two RCTs [28,29] have studied the usefulness of GM in DIC. These studies, which were small in size, did not demonstrate any significant difference in the outcome or improvement of DIC between the patients treated with GM and those without (Level 2b).

Two randomized non-blind clinical trials evaluating the use of GM (Level 2b)[30] and NM (Level 2b)[31] in the treatment of DIC have been performed over the past twenty years. No significant difference was observed in the outcome or improvement of DIC between GM or NM and UFH. Because these older clinical trials were non-blinded, objectivity may thus have been reduced. GM and NM are recommended in cases in which hemorrhaging immediately after an operation or similar event is remarkable and also in cases in which there is the high possibility of hemorrhaging due to a marked decrease in platelet counts, etc. Neither GM nor NM improved the mortality but JMHW approved those drugs for DIC treatment since they resulted in less deterioration of bleeding.

3) Physiologic protease inhibitors

Physiologic protease inhibitors including AT [3], APC [4], TFPI [5], and TM [18] have recently been evaluated for their efficacy in the treatment of severe sepsis and DIC. AT, APC, and TM exist in biological conditions to control intravascular clotting. Physiological protease inhibitors can be used for the treatment of DIC. Only AT has been approved for DIC treatment by Japanese Ministry Health and Welfare as of 2007 and limited use of TM has been approved as of 2008.

a) Antithrombin (AT)

Level of recommendation: B1 in general, B1 in organ dysfunction type, B2 in asymptomatic/hemorrhagic/thrombotic type. AT is a single-stranded glycoprotein with a molecular weight of ca. 59,000, it is synthesized in the liver and inhibits thrombin as well as activated factors X, IX, VII, XI, and XII [32]. The blood level of AT is markedly reduced in patients with diseases such as sepsis due to consumption by accelerated coagulation, decreased hepatic production, metabolism by elastase, and extravascular leakage due to increased endothelial permeability [33]. AT has recently attracted attention due to a possible anti-inflammatory effect at high doses in addition to

its anticoagulant effect. It influences the vascular endothelial function by altering the production of prostacyclin [34].

Clinical studies of AT have been extensively performed in patients with severe sepsis [3,35–39](Level 1b~2b), and the level of recommendation was determined based on the results. The survival rate on day 28 of treatment was not improved in the KyberSept trial [3](Level 1b), which was a multicenter, double-blind, phase III study performed in 2,314 patients with severe sepsis (a total of 30,000 IU was administered over 4 days). However, an improvement of the survival rate on day 90 was shown in patients without concomitant heparin treatment by subgroup analysis, this agreed with the results of previous phase II studies supporting the efficacy of AT [40–44] (Level 2b). A relatively small-scale RCT [42](Level 2b) was performed in 40 patients with severe sepsis after the KyberSept trial, significant improvement of the coagulation index was achieved by supplementing AT activity to 120%. Furthermore, significant improvement of the survival rate (25.4% vs. 40.0%, $p = 0.02$) was shown in DIC patients by investigation of the patients without concomitant heparin treatment in the KyberSept trial [43]. A meta-analysis of DIC patients with sepsis also demonstrated improvement of the outcome by administration of AT [44] (Level 2a). The above findings suggest that AT administration for patients who have DIC associated with sepsis is useful not only for shortening the duration of DIC symptoms, but also for improving the outcome. However, the optimum dose and dosing period still need to be determined. It was reported that bleeding may be exacerbated and improvement of the outcome may be reversed by administration of AT to patients who have DIC associated with sepsis and are concomitantly receiving heparin (even at a low dose of 10,000 IU/day).

b) Other protease inhibitor

APC has an anticoagulatory effect via the inactivation of FVIIIa and FVa and it also activates protease-activated receptor-1 (PAR-1) to inhibit inflammation and apoptosis. There are 2 types of APC: plasma derived APC and rAPC. In RCT for severe sepsis (PROWESS trial; Level 1b) [4] rAPC ($n = 850$) significantly reduced the mortality of septic patients including 22.4% of those with DIC in comparison to the placebo group ($n = 850$). In addition, the plasma D-dimer and the serum IL-6 levels were significantly lower in the APC treated group than in the placebo group. The US Food and Drug Administration has approved rAPC for the treatment of severe sepsis, thus suggesting that anticoagulant therapy is recommended in DIC, but rAPC is not approved by the Japanese Ministry Health and Welfare as of 2009. In RCTs of plasma derived APC for DIC [17](Level 2b), the mortality, deterioration of bleeding symptoms, and hemostatic molecular markers were significantly lower in the APC group ($n = 63$) than in UFH group ($n = 69$).

TM binds thrombin and the thrombin-TM complex activates PC to APC. TM also binds high-mobility group-B1 (HMGB-1), thus inhibiting the inflammatory process. In RCT for rTM in sepsis and hematopoietic malignancy ($n = 234$)[18](Level 2b), rTM significantly improved DIC and its bleeding symptoms in comparison to UFH. As a result, TM appears to be an effective drug for the treatment of DIC. Both rAPC and plasma derived APC have not yet been approved, while rTM has been approved with various restrictions by Japanese Ministry Health and Welfare as of April 30, 2009.

3. Anti-fibrinolytic or fibrinolytic therapy. In DIC due to infection, the plasminogen activator inhibitor-I (PAI-I) levels are increased and fibrinolysis is inhibited.

1) Anti-fibrinolytic therapy (tranexamic acid and e-amino caproic acid)

Level of recommendation: D in general; C in solid cancer, aortic aneurysm, Kasabach-Merrit syndrome, acute prmyelocytic leukemia (APL) without ATRA; D in APL with ATRA; It is recommended only in the case of severe bleeding tendency due to enhanced fibrinolysis and it is required to be combined with a anticoagulation therapy under consultations with a specialist. One molecule of tranexamic acid is decomposed into two molecules of e-amino caproic acid in blood. Both these drugs have a lysine-like structure which binds to the lysine binding site of plasminogen, thus preventing the plasminogen to bind on fibrinogen, following anti-fibrinolytic activity. In addition, the continuous administration of these drugs reduces the plasma concentration of plasminogen.

As anti-fibrinolytic therapy for DIC may inhibit the dissolution of the thrombus by activation of fibrinolysis, this therapy is considered to be contraindicated in DIC, especially in DIC due to infection. An inadequate anti-fibrinolytic therapy causes organ failure and systemic thrombosis. Anti-fibrinolytic therapy is effective in DIC with enhanced fibrinolysis and the combination with heparin is necessary in this case. NM, which has both anticoagulant and anti-fibrinolytic effects, is also useful in DIC with enhanced fibrinolysis. In DIC with suppressed fibrinolysis, such as DIC due to severe sepsis, anti-fibrinolytic therapy is contraindicated. APL has hyperfibrinolytic DIC, but APL treated with ATRA does not have a hyperfibrinolytic state. Fatal thrombosis has been reported in APL treated with ATRA [45,46] and antifibrinolytic therapy is contraindicated in this DIC. 2) Fibrinolytic therapy (tissue type plasminogen activator (t-PA), urokinase type PA (UK).

Level of recommendation: D. Plasminogen activator (PA) converts plasminogen to plasmin, the plasmin demonstrates fibrinolytic action, and dissolves the fibrin clot (thrombus). Although plasmin has a high affinity with fibrin to selectively dissolve it, elevated plasmin generation causes fibrinogenolysis. However, the affinity with fibrin is higher in t-PA than in u-PA. In addition, t-PA also causes fibrinogenolysis, as advanced DIC often demonstrates enhanced fibrinolysis and consumption coagulopathy. However, fibrinolytic therapy is theoretically attractive in patients with DIC due to an infection, however, this therapy increases the risk of hemorrhage.

4. Transfusion. The treatments for underlying disease and anticoagulant therapy are essential in DIC treatment, therefore, the transfusion of platelet concentrate (PC) or fresh frozen plasma (FFP) without the above treatment should be reserved. This treatment should be carried out in acute DIC with severe bleeding or hemostatic abnormality such as APL and aneurysm, but it should not be done in chronic DIC or septic DIC with suppressed fibrinolysis. As the guideline for blood transfusion tend to differ somewhat among various countries, blood transfusion should therefore be performed while carefully referring to each country's guidelines for blood transfusion [47–49].

1) Fresh frozen plasma (FFP)

Level of recommendation: consensus in severe bleeding, operation or thrombotic thrombocytopenic purpura (TTP); it is necessary to act according to the domestic guidelines for blood transfusion in principle. The main purpose of administering of FFP is to replenish several clotting factors and APTT, PT, and fibrinogen values should be monitored before the administration of FFP. The administration of FFP is recommended in patients with more than 2.0 of PT-INR, a 2-fold prolongation of APTT and less than 100 mg/dl of fibrinogen.

2) Platelet concentrates (PC)

Level of recommendation: consensus in severe bleeding or operation, D in TTP or HIT; principally limited to patients with platelets less than 50,000/μL. Although there is usually no fear of hemorrhaging in cases with more than 50000/μL of platelets, platelet count dramatically changes in DIC. In cases in which a bleeding tendency is obvious, as in an operation, as well as in cases in which the platelet count rapidly decreases to less than 50000/μL, PC infusion is considered. However, platelet transfusion should be administered very carefully when organ failure is obvious. The administration of PC is prohibited in patients with HIT, while it should only be administered after careful consideration in patients with markedly low ADAMTS13 levels (less than 3%) such as TTP [50].

5. Treatment of the three types of DIC. DIC is classified as follows: asymptomatic type, marked bleeding type, and organ failure type. The appropriate treatment differs based on the type (Table 2).

Table 2
Recommended DIC treatment for each symptom.

Classification (symptom)			Treatment for underlying disease	Anticoagulation therapy					Anti-fibrinolytic therapy	Fibrinolytic therapy	Blood transfusion	
				UFH	LMWH	DS	SPI	AT			FFP	PC
General			○	C	B_2	C	B_2	$B_1^{\#}$	D	D	○*	○*
asymptomatic	blood transfusion	not necessary	○	C	B_2	C	B_2	$B_2^{\#}$	D	D		
		necessary	○	C	B_2	C	B_2	$B_2^{\#}$	D	D	B_2^*	B_2^*
bleeding	slightly		○	C	B_2	C	B_2	$B_2^{\#}$	D	D		
	severe		○	D	D	D	B_1	$B_2^{\#}$	C$^{\$}$	D	○*	○*
organ failure			○	C	B_2	C	B_2	$B_1^{\#}$	D	D		
complication	major thrombosis		○	B_2	B_1	B_2	C	$B_2^{\#}$	D	?		
	TTP		○	C	B_2	C	B_2	$B_2^{\#}$	D	D	○	D
	HIT		○	D	D	D	B_2	$B_2^{\#}$	D	D		D

○; consensus, #; limited in patients with less than 70% of AT, *; according to the guideline for blood transfusion, ?; consultation with specialist for fibrinolytic therapy, $; consultation with specialist for anti-fibrinolytic therapy, UFH; unfractionated heparin, LMWH; low molecular weight heparin, DS; danaparoid sodium, GM; gabexate mesilate, NM; nafamstat mesilate, AT; antithrombin, FFP; fresh frozen plasma, PC; platelet concentrates, TTP; thrombotic thrombocytopenic purpura, HIT, heparin induced thrombocytopenia.

1) Asymptomatic type: Marked clinical symptoms of DIC not observed but laboratory findings confirm DIC. Early treatment of DIC is required in this phase. LMWH, SPI as GM, NM, and AT are considered as B2 and UFH and DS are considered as C. Even though AT is reported to be effective in severe septic patients with a predicted mortality of 30% -60% [45], AT is expensive for the treatment of mild DIC and LMWH is the cheapest among the drugs described by recommendation B.

2) Marked bleeding type: LMWH, SPI, and AT are considered as B2, but LMWH, UFH, and DS are not recommended in case of fatal bleeding. In severe or life threatening bleeding, SPI (B1) and blood transfusions such as a fresh frozen plasma (FFP) and platelet concentrate (PC) (Consensus) are recommended.

3) Organ failure type: This type includes capillary leak syndrome and septic shock usually due to sepsis. In a meta-analysis, AT significantly improved the mortality in moderate severe sepsis (Level 1a)[51]. AT is recommended (B1). AT is approved for use in patients with less than 70 % of AT in Japan and the measurement of AT is required in septic DIC.

6. Complications. Patients with DIC are frequently associated with thrombosis (deep vein thrombosis, pulmonary embolism and acute myocardial infarction). These patients require strong anticoagulant therapy with LMWH, UFH, and DS. Rarely, DIC patients are associated with thrombotic thrombocytopenic purpura (TTP) and heparin induced thrombocytopenia (HIT); in these cases, the transfusion of PC should be done carefully. LMWH and UFH are contraindicated for HIT.

Conflict of interest

Iba T had a grant from Organon USA INC and Wada H was a member of the drug monitor committee for recombinant FVIIa (Novo Nordisk) in cerebral bleeding and trauma.

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