PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

International Consensus Statement 2013
Guidelines According to Scientific Evidence

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European Venous Forum
North American Thrombosis Forum
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Union Internationale du Phlebologie

Heparin-Induced Thrombocytopenia

Chapter 19

General Considerations

- **Heparin-induced thrombocytopenia (HIT) is an important adverse effect of heparin**
- **HIT is a life-threatening, prothrombotic, immune-mediated coagulopathy caused by antibodies that bind to the complex of platelet factor 4 (PF4) and heparin[1]**
- **HIT occurs most frequently in cardiac surgery, orthopedic surgery, and medical patients, but can be found in other patient populations and clinical settings[2-15]**

1. Arepally G, Cines DB. Clin Rev Allergy Immunol 1998; 16:237-47.
2. Liu JC, et al. Am J Cardiol 2002; 89:979-81.
3. Verma AK, et al. Pharmacotherapy 2003; 23:745-53.
4. Warkentin TE, et al. Blood 2000; 96:1703-8.
5. Warkentin TE, et al. Arch Intern Med 2003; 163:2518-24.
6. Girolami B, et al. Blood 2003; 101:2955-9.
7. Martel M, et al. Blood 2005:2710.
8. Smythe MA, et al. Chest 2007; 131:1644-9.
9. Crespo EM, et al. Am Heart J 2009; 157:651-7.
10. Walls JT, et al. Ann Thorac Surg 1992; 53:787-91.
11. Matsuo T, et al. Thromb Res 2005; 115:475-81.
12. Mehta R, Golichowski A. J Thromb Haemost 2004; 2:1665-6.
13. Campbell IA, et al. Br Med J 2007; 334:674-80.
14. Skedgel C, et al. J Bone Joint Surg Am 2007; 89:819-28.
15. Kawano H, et al. Cerebrovasc Dis 2008; 26:641-9.

General Considerations

- **Progression to overt thrombosis is the most serious complication of patients with HIT as it often leads to amputation or death[1-4]**
- **Spontaneous bleeding and petechiae have been reported only rarely**
- **HIT Type I is a transient but self-limited fall in platelet count in up to 30% of treated patients**
- **This occurs through a non-immunological mechanism in the first 24 hours of receiving heparin and resolves within 24-48 hours[5]**

1. Warkentin TE, Kelton JG. Am J Med 1996; 101:502-7.
2. Wallis DE, et al. Am J Med 1999; 106:629-35.
3. Elalamy I, et al. Thromb Res 2009; 124:554-9.
4. Nand S, et al. Am J Hematol 1997; 56:12-6.
5. Brieger DB, et al. J Am Coll Cardiol 1998; 31:1449-59.

General Considerations
Frequency of HIT

- The frequency of HIT is influenced by several factors
- The risk of developing HIT is higher from exposure to UFH (bovine > porcine) than LMWH and is more duration- than dose-dependent[1-10]
- HIT can occur with a higher frequency in LMWH treated patients who were previously exposed to UFH[11]
- HIT due to LMWH is as severe as UFH induced HIT[4]

1. Martel M, et al. Blood 2005:2710.
2. Smythe MA, et al. Chest 2007; 131:1644-9.
3. Francis JL, et al. Ann Thorac Surg 2003; 75:17-22.
4. Gruel Y, et al. Br J Haematol 2003; 121:786-92.
5. Warkentin TE, et al. N Engl J Med 1995; 332:1330-5.
6. Levine RL, et al. Chest 2006; 130:681-7.
7. Lindhoff-Last E, et al. Br J Haematol 2002; 118:1137-42.
8. Ban-Hoefen M, et al. Thromb Res 2009; 124:189-92.
9. Walenga JM, et al. Curr Opin Pulm Med 2005; 11:385-91.
10. de Maistre E, et al. J Vasc Surg 2009; 49:596-601.
11. van Dongen CJ, et al. J Thromb Haemost 2005; 3:939-42.

General Considerations
Frequency of HIT

- **HIT can occur with prophylactic doses of heparin and heparin from exogenous sources[1,2]**
- **Preventive measures include:**
  - The use of LMWH, fondaparinux, and non-heparin anticoagulants rather than UFH for post-surgical prophylaxis
  - The use of porcine rather than bovine UFH
  - Avoiding unnecessary and prolonged exposure to UFH

1. de Maistre E, et al. J Vasc Surg 2009; 49:596-601.
2. Kadidal VV, et al. J Intern Med 1999; 246:325-9.

General Considerations
Diagnosis of HIT

- **Diagnosis of HIT is based on clinical findings and platelet count**
- **If recently treated with heparin, HIT should be suspected on the basis of a 30% decrease in platelet count from baseline in the absence of other reasons for thrombocytopenia[1-3]**
- **The diagnosis can be made if the platelet count reduction is 50% of baseline, assuming no other reasons for thrombocytopenia[1-3]**

1. Arepally G, et al. Clin Rev Allergy Immunol 1998; 16:237-47.
2. Linkins LA, et al. Ann Intern Med 2003; 139:893-900.
3. Baglin T, et al. Br J Haematol 2010; 149:209-20.

General Considerations
Diagnosis of HIT

- **An abrupt decrease in platelet count in the absence of other etiologies, that does not result in thrombocytopenia, and unexplained thrombosis are also characteristics of HIT[1-3]**
- **Symptoms typically appear 4 to 14 days after exposure to UFH or 8 to 14 days after exposure to LMWH[4-6]**
- **Patients who received heparin within the prior 100 days can have an immediate, rapid-onset HIT when restarting UFH or LMWH[5,6]**

1. Arepally G, et al. Clin Rev Allergy Immunol 1998; 16:237-47.
2. Linkins LA, et al. Ann Intern Med 2003; 139:893-900.
3. Baglin T, et al. Br J Haematol 2010; 149:209-20.
4. Gruel Y, et al. Br J Haematol 2003; 121:786-92.
5. Warkentin TE, Kelton JG. N Engl J Med 2001; 344:1286-92.
6. Lubenow N, et al. Chest 2002; 122:37-42.

General Considerations
Diagnosis of HIT

- **Delayed-onset HIT has been observed with symptoms appearing several days after discontinuation of UFH[1,2]**
- **The diagnosis of HIT is difficult in patients after surgery, particularly after cardiac surgery[3-5]**
  - HIT should be suspected if the platelet count recovery in the immediate post-operative period is interrupted by a sudden and marked platelet count decrease 5-10 days post-operation
  - HIT cannot be definitely excluded in patients with a monophasic pattern of persistent post-operative thrombocytopenia

1. Arepally G, et al. Clin Rev Allergy Immunol 1998; 16:237-47.
2. Rice L, et al. Ann Intern Med 2002; 136:210-5.
3. Pouplard C, et al. Br J Haematol 2005; 128:837-41.
4. Lillo-LeLouet A , et al. J Thromb Haemost 2004; 2:1882-8.
5. Selleng K, et al. J Thromb Haemost 2009; 8:27-29.

General Considerations
Diagnosis of HIT

- A clinical presentation of HIT that can be challenging is the patient with only mild thrombocytopenia receiving heparin or LMWH
- These patients are to be individually assessed for their risk of having HIT
- The level of risk will determine whether or not to continue heparin/LMWH treatment while laboratory testing is sent to confirm the diagnosis
- Clinical scoring systems are available and continue to be developed to assist in the diagnosis of HIT[1-4]

1. Lillo-LeLouet A , et al. J Thromb Haemost 2004; 2:1882-8.
2. Lo GK, et al. J Thromb Haemost 2006; 4:759-65.
3. Cuker A, et al. J Thromb Haemost 2010; 8:2642-50.
4. Messmore HL, et al. Clin Appl Thromb Hemost 2011; 17:197-201.

General Considerations
Diagnosis of HIT

- **Clinical diagnosis of HIT should be confirmed by a laboratory assay that detects heparin-dependent antibodies**
- **Pathologic HIT immune complexes are composed of the PF4-heparin complex bound to an immunoglobulin G (IgG)[1-5]**
- **These complexes bind to platelet Fcγlla receptors (CD 32), inducing platelet activation, aggregation, and generation of platelet microparticles[6,7]**

1. Amiral J, et al. Thromb Haemost 1992; 68:95-6.
2. Greinacher A, et al. Thromb Haemost 1994; 71:247-51.
3. Visentin GP, et al. J Clin Invest 1994; 93:81-8.
4. Horsewood P, et al. Br J Haematol 1996; 95:161-7.
5. Newman PM, Chong BH. Blood 2000; 96:182-7.
6. Kelton JG, et al. Blood 1988; 72:925-30.
7. Warkentin TE, et al. Blood 1994; 84:3691-9.

General Considerations
Diagnosis of HIT

- IgA and IgM have also been identified in HIT patients[49]
- HIT antibodies provoke leukocyte and endothelial cell activation that augment both the hypercoagulable and inflammatory states[1-7]
- The combined cellular activation leads to a burst of thrombin generation[8]
- Of all patients at risk of thrombosis, those with HIT are at highest risk (>30%)[9]

1. Arepally G, et al. Clin Rev Allergy Immunol 1998; 16:237-47.
2. Visentin GP, et al. J Clin Invest 1994; 93:81-8.
3. Fareed J, et al. Semin Thromb Hemost 1999; 25 Suppl 1:37-42.
4. Pouplard C, et al. Blood 2001; 97:3300-2.
5. Blank M, et al. Int Immunol 2002; 14:121-9.
6. Walenga JM, et al. Sem Thromb Hemost 2004; 30, Suppl.1:57-67.
7. Walenga JM, et al. J Thromb Thrombolysis 2000; 10 Suppl 1:13-20.
8. Tardy B, et al. Thromb Haemost 1998; 80:530.
9. Linkins LA, et al. Ann Intern Med 2003; 139:893-900.

General Considerations
Diagnosis of HIT

- **Non-drug factors also influence the risk of developing HIT and related clinical outcomes[1-4]**
  - Type of surgery, severity of trauma, severity of thrombocytopenia, renal impairment, low cardiac output, and timing of first anticoagulant dose
- **The association of HIT antibodies, in the absence of thrombocytopenia and thrombosis, with future cardiovascular and other thrombotic events has been reported and remains under investigation[5]**

1. Kelton JG, et al. Blood Coagul Fibrinolysis 2008; 19:471-5.
2. Lubenow N, et al. Blood 2010; 115:1797-803.
3. Assman A, et al. Thorac Cardiovasc Surg 2010; 58:463-7.
4. Warkentin TE, et al. J Thromb Haemost 2010; 8:504-12.
5. Stribling WK, et al. Am Heart J 2007; 153:900-6.

General Considerations
Diagnosis of HIT

- **Two types of laboratory assays that detect heparin-dependent antibodies:[1-4]**
  - Platelet function tests (serotonin release and platelet aggregation assays)
  - Immunoassays that detect antibodies to the PF4-heparin complex
- **Each test has particular performance characteristics, and provides unique information[5-7]**

1. Sheridan D, et al. Blood 1986; 67:27-30.
2. Greinacher A, et al. Thromb Haemost 1991; 66:734-6.
3. Chong BH, et al. Thromb Haemost 1993; 69:344-50.
4. Prechel M, et al. Methods Mol Biol 2010; 663:133-56.
5. Walenga JM, et al. Clin Appl Thromb Hemost 1999; 5:21-7.
6. Greinacher A, et al. Transfusion 1994; 34:381-5.
7. Walenga JM, et al. Semin Thromb Hemost 1999; 25, Suppl. 1:43-9.

General Considerations
Diagnosis of HIT

- **Platelet function assays that use washed platelets have a better sensitivity than plasma-based assays, but false negative results can still be obtained**
- **Immunoassays have a high rate of positive results that are not always associated with clinical HIT[1-4]**
- **For immunoassays:[5-10]**
  - The option to report the titre results and utilizing the high heparin concentration confirmatory step are gaining favor as these provide a closer correlation to the risk of thrombosis and mortality in patients with HIT

1. Walenga JM, et al. Clin Appl Thromb Hemost 1999; 5:21-7.
2. Pouplard C, et al. Am J Clin Pathol 1999; 111:700-6.
3. Lindhoff-Last E, et al. Thromb Res 2000; 97:387-93.
4. Ahmad S, et al. Thromb Res 2002; 108:49-55.
5. Ban-Hoefen M, et al. Thromb Res 2009; 124:189-92.
6. Levine RL, et al. J Thromb Thrombolysis 2010; 30:142-8.
7. Zwicker JI, et al. J Thromb Haemost 2004; 2:2133-7.
8. Whitlatch NL, et al. Thromb Haemost 2008; 100:678-84.
9. Whitlatch NL, et al. Blood 2010; 116:1761-6.
10. Warkentin TE, et al. J Thromb Haemost 2008; 6:1304-12.

General Considerations
Direct Thrombin Inhibitors

- **Clinical trials and experience have shown that argatroban and lepirudin to be safe and effective for reducing the risk of thrombosis and associated morbidity/mortality in patients with HIT[1-9]**
- **These drugs do not cross-react with HIT antibodies**
- **Development of antibodies to lepirudin has been observed in approximately 50% of patients after 10 days of treatment[10,11]**

1. Lewis BE, et al. Arch Intern Med 2003; 163:1849-56.
2. Lewis BE, et al. Circulation 2001; 103:1838-43.
3. Guyatt G, et al. Chest 2006; 129:174-81.
4. Madabushi R, et al. J Clin Pharmacol 2011; 51:19-28.
5. Gray A, et al. Clin Appl Thromb Hemost 2007; 13:353-61.
6. Hursting MJ, et al. Nephron Clin Pract 2008; 109:80-94.
7. Ilahi OA, et al. Arthroscopy 2005; 21:727-30.
8. Greinacher A, et al. Circulation 1999; 100:587-93.
9. Greinacher A, et al. Circulation 1999; 99:73-80.
10. Greinacher A, et al. Circulation 2003; 108:2062-5.
11. Eichler P, et al. Blood 2000; 96:2373-8.

General Considerations
Direct Thrombin Inhibitors

- **Dose adjustments for argatroban in specific populations and for lepirudin in general have been recently recommended[1-6]**
- **Desirudin, with the advantage of SQ dosing, has been successfully used in a limited number of patients with HIT[7,8]**

1. Madabushi R, et al. J Clin Pharmacol 2011; 51:19-28.
2. Levine RL, et al. Chest 2006; 129:1167-75.
3. Hursting MJ, Soffer J. Drug Saf 2009; 32:203-18.
4. Lubenow N, et al. J Thromb Haemost 2005; 3:2428-36.
5. Tardy B, et al. Blood 2006; 108:1492-6.
6. Tschudi M, et al. Blood 2009; 113:2402-9.
7. Boyce SW, et al. Am J Ther 2011; 18:14-22.
8. Sukhija R, et al. Am J Cardiol 2005; 95:695-6.

General Considerations
Direct Thrombin Inhibitors

- **Bivalirudin, with a short half-life and enzymatic degradation, has been used for anticoagulation of HIT patients during cardiac surgery[1-3]**
- **DTIs have also been used successfully in HIT patients requiring invasive cardiac procedures[4-6]**
- **DTIs should be treated as individual drugs as each has its own pharmacologic characteristics**

1. Kiser TH, et al. Pharmacotherapy 2008; 28:1115-24.
2. Koster A, et al. Ann Thorac Surg 2007; 83:572-7.
3. Comp PC, et al. Orthopedics 1998; 21:1123-8.
4. Liu JC, et al. Am J Cardiol 2002; 89:979-81.
5. Mahaffey KW, et al. J Invasive Cardiol 2003; 15:611-6.
6. Lee MS, et al. Int J Cardiol 2010; 152:369-74.

General Considerations

- **Danaparoid, a heparinoid, has been used to treat HIT patients with success (Grade B) but there are reports that danaparoid cross-reacts with some HIT antibodies leading to treatment failures[1-7]**
- **Fondaparinux, a pentasaccharide, has shown to be useful for the management of patients with HIT through several small published case series[8-11]**
- **LMWH can cross-react with most HIT antibodies and is contraindicated for use in patients with HIT[12-14]**

1. Magnani HN. Thromb Haemost 1993; 70:554-61.
2. Chong BH, et al. Thromb Haemost 2001; 86:1170-5.
3. Lindhoff-Last E, et al. Thromb Haemost 2005; 93:63-9.
4. Farner B, et al. Thromb Haemost 2001; 85:950-7.
5. Kodityal S, et al. Eur J Haematol 2003; 71:109-13.
6. Haas S, et al. Clin Appl Thromb Hemost 1999; 5:52-9.
7. Tardy B, et al. Thromb Haemost 1998; 80:530.
8. Hooker JA, et al. J Bone Joint Surg Am 1999; 81:690-6.
9. Lobo B, et al. Thromb Haemost 2008; 99:208-14.
10. Grouzi E, et al. Clin Appl Thromb Hemost 2010; 16:663-7.
11. Warkentin TE, et al. J Thromb Haemost 2011; 9:2389-96.
12. Walenga JM, et al. Curr Opin Pulm Med 2005; 11:385-91.
13. Greinacher A, et al. Thromb Haemost 1995; 74:886-92.
14. Walenga JM, et al. Clin Appl Thromb Hemost 1996:S21-7.

General Considerations

- **Vitamin K antagonists (VKAs) are recommended for long-term treatment of HIT associated thrombosis[1]**
- **VKAs are not recommended for use in the acute phase of HIT due to their potential to intensify the prothrombotic state from a transient protein C deficiency[2,3]**
- **VKAs should be initiated when platelet counts have normalized to a steady state then brought on under bridging with a DTI[4-6]**

1. Linkins LA, et al. Ann Intern Med 2003; 139:893-900.
2. Warkentin TE, et al. Ann Intern Med 1997; 127:804-12.
3. Srinivasan AF, et al. Arch Intern Med 2004; 164:66-70.
4. Hursting MJ, et al. Clin Appl Thromb Hemost 2005; 11:279-87.
5. Bartholomew JR, Hursting MJ. J Thromb Thrombolysis 2005; 19:183-8.
6. Walenga JM, et al. Clin Appl Thromb Hemost 2008; 14:325-31.

General Considerations

- **There is emerging evidence that the newly developed small molecule anticoagulants including apixaban, dabigatran, edoxaban, otamixaban, and rivaroxaban may become new immediate and long-term treatment options for thrombosis in patients with HIT[1]**

1. Hooker JA, et al. J Bone Joint Surg Am 1999; 81:690-6.

Recommendations
Heparin-Induced Thrombocytopenia

- **For the first 14 days of treatment, platelet counts should be performed every 2-3 days in patients treated with LMWH and daily if treated with UFH, if the patient's risk of developing HIT is high**
  - Level of evidence: Moderate
- **Laboratory testing should be performed when there is a strong suspicion of HIT**
  - Level of evidence: Moderate
- **UFH and LMWH should be stopped when the diagnosis of HIT is strongly suspected or confirmed**
  - Level of evidence: High

Recommendations
Heparin-Induced Thrombocytopenia

- **Due to the strong hypercoagulable state and high risk of thrombosis associated with HIT, it is recommended that all HIT patients be treated with a non-heparin anticoagulant such as argatroban, lepirudin, or danaparoid**
  - Level of evidence: Moderate
- **Fondaparinux may be considered as a second-line agent in the management of patients with suspected HIT**
  - Level of evidence: Low
- **LMWH is contraindicated in patients with HIT**
  - Level of evidence: Moderate

Recommendations
Heparin-Induced Thrombocytopenia

- **For long-term anticoagulation, a VKA can be used. To avoid warfarin-induced limb gangrene/skin necrosis in patients with HIT, the VKA should only be administered after rise of platelet counts with substantial recovery to >100 x 109/L or to pre-HIT values**
  - Level of evidence: Low
- **For HIT patients undergoing coronary artery interventional procedures, bivalirudin or argatroban anticoagulation is recommended**
  - Level of evidence: Moderate