QUESTION 78 Haematology/Cardiology

A 72-year-old man with a history of coronary artery bypass grafting is admitted with biventricular failure. His full blood examination is normal on admission. In addition to therapy for cardiac failure, he receives thromboprophylaxis with subcutaneous unfractionated heparin, 5000 units twice daily. On day 8 of admission, he complains of left leg pain and an ultrasound shows extensive thrombosis extending from the popliteal to the external iliac veins. His full blood examination now reveals thrombocytopenia (platelets 35 x 10^9/L [150-396]) and a test for heparin-induced thrombocytopenia by enzyme-linked immunosorbent assay (ELISA) is positive. There is no current evidence of bleeding. In addition to stopping the heparin, which of the following is the most appropriate immediate treatment option?

A. Observation.  
B. Dalteparin.  
C. Platelet transfusion.  
D. Intravenous immunoglobulin.  
E. Danaparoid.

Suspected HIT:
1) Thrombocytopenia,  
2) thrombosis with thrombocytopenia,  
3) a plt count which has fallen by > 50% or  
4) necrotic skin lesions at injection sites in a pt started on heparin within the preceding 5 to 10 days.

Clinical manifestation:

Onset: 4 to 10days after initiation of heparin, 2 weeks is unusual  
Early onset may be seen if receive heparin in prev 3 to 4 mths  
Delayed onset: occurs after heparin has been withdrawn (average 9 days post withdrawal)

1) spontaneous bleeding is unusual as thrombocytopenia rarely drops below 30-60,000/mL  
2) Thrombosis  
   - venous & arterial thrombosis  
   - mechanism of hypercoagulable state unknown  
   - major manifestations of venous thrombosis is DVT and PE, venous limb gangrene, cerebral sinus thrombosis  
   - arterial thrombosis- less common - stroke, MI, limb ischemia from peripheral arterial ooclusion or organ infarction. Thrombosis tend to be platelet rich and therefore these clots are "white" due to platelet aggregates → "white clot syndrome"  
3) Skin necrosis  
   - affected areas usually fat -rich : abdomen  
   - lesions similar to warfarin-induced skin necrosis, deficiencies of natural anticoargulants are not present

Pathophysiology:

Antibody response: IgG and Ig M antibodies provoked by heparin, complex of heparin bound to platelet factor 4 (PF4)  
IgG antibody directed against the heparin-PF4 complex binds platelets through the Fc receptor, leading to platelet activation and micro-particle formation.  
Platelet rich thrombi form at sites of preexisting pathology or sites of endothelial cell injury

Diagnostic testing:

Clinical diagnosis:  
Unexplained thrombocytopenia
Thrombosis ass with thrombocytopenia
A plt count fallen 50% or more from prior value
Necrotic skin lesions at heparin injection sites

Diagnostic test: serotonin release assays (gold standard sensitivity 100%, specificity 97%), heparin-induced platelet aggregation assays and solid phase immunoassays

Treatment
1) Cessation of all exposure to heparin
2) LMW heparin should be avoided due to cross reactivity with heparin induced antibodies
3) Patients remain at risk of thrombosis and therefore require ongoing anticoagulation

Choices
a) lepirudin (recombinant hirudin)
b) bivalirudin
c) argatroban
d) danaparoid
   i. 10% cross reactivity between danaparoid and the antibody responsible for HIT
   ii. Persistence of, or recurrence of thrombocytopenia without thrombosis in 6.5% of pts switched from heparin to danaparoid.
   iii. Long half life and therefore need to measure anti-Xa levels to monitor its anticoagulant effect and the absence of a reversing agent

To continue until platelet count recovers

Back to the question:
Its not the answer A, Observation because they remain at risk of further thrombosis and therefore need ongoing anticoagulation.

Option B daltaparin (low molecular weight heparin)
Cross reactivity with antibodies and therefore should not be used

Option C Platelet transfusion
Spontaneous bleeding begins at platelet count below 40,000/mcL while severe spontaneous bleeding seen at plt counts below 10,000. With HIT, there is low bleeding and giving platelets may increase the risk of new thromboembolic lesions

Option D
IV immunoglobulins have not much evidence that it works.

Note: Warfarin should not be given to patients who already have HIT until the thrombocytopenia resolves. Warfarin in the absence of other anticoagulants should be avoided in patients with HIT until the platelet count rises above 100 × 10^9/L. Because of its early effects on protein C, warfarin can precipitate venous limb gangrene and limb loss in the extreme prothrombotic milieu of type 2 HIT.

Answer E Danaparoid.