QUESTION 20 Clotting
A 65-year-old man presents to the emergency department with ischaemic chest pain. No abnormalities are noted on examination apart from mild hypotension.

His full blood examination shows:
- haemoglobin: 125 g/L [128-175]
- white cell count: $10.2 \times 10^9$ /L [3.9-12.7] (normal white cell differential)
- platelets: $180 \times 10^9$ /L [150-396]

Coagulation investigations show:
- activated partial thromboplastin time (APTT): 100 seconds [26-38]
- APTT 1:1 mix (patient: normal plasma): 52 seconds
- prothrombin time-international normalised ratio (PT-INR): 1.2 [1.0-1.3]
- thrombin clotting time (TCT): 200 seconds [<24]
- fibrinogen: 4.5 g/L [2.0-4.0]
- reptilase time: 18 seconds [<24]

The most likely cause of the coagulation test abnormalities is:
A. disseminated intravascular coagulation.
B. administration of low-molecular weight heparin.
C. administration of thrombolytic agent.
D. lupus inhibitor.
E. administration of unfractionated heparin.

Coagulation pathways

<table>
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<tr>
<th>Test</th>
<th>Pathway</th>
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<tr>
<td>APTT</td>
<td>Intrinsic and common pathway</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Extrinsic and common pathway</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Final step fibrinogen to fibrin</td>
</tr>
<tr>
<td>Last step of fibrin crosslinked through action of factor XIII not tested</td>
<td></td>
</tr>
</tbody>
</table>
Prothrombin time

- Extrinsic and common pathway
- Factor VII, II, X, V and fibrinogen
- Expressed as ratio INR

Causes of prolonged PT

1. Warfarin
2. Vit K deficiency
3. Factor II, VII, V and fibrinogen deficiency
4. Liver disease

Warfarin
Mediated by inhibition of Vit K dependent factors – II, VII, IX & X

APTT

- Monitor intrinsic coagulation pathway and final common pathway
- Monitor heparin therapy

Causes of prolonged APTT

1. Hepain
2. von Willebrand disease
3. Lupus anticoagulant
4. Deficiency of factors VIII, IX or XI, XII, prekallikrein or HMW kininogen

Heparin
- Activates antithrombin (AT), which irreversibly inactivates prothrombin, factor Xa, factors XIIa, XIa and IXa

LMWH
- Inactivate factor Xa
- No need for monitoring because the anticoagulant response to a fixed dose of LMWH is highly correlated with patient’s body weight
- Monitoring via anti-factor Xa activity

Thrombin time

- Final step of clotting pathway (fibrinogen to fibrin)

Causes of prolonged TT

1. Hepain or hepin like compounds (danaparoid)
2. Presence of fibrin/fibrinogen degradation products
3. Disorders of fibrin
4. High concentration of serum proteins (myeloma. Amyloidosis)

Reptilase time

- Reptilase is an enzyme similar to thrombin that is found in venom of Bothrops snakes
- Differs from thrombin by generating fibrinopeptide A but not fibrinopeptide B from fibrinogen and by resisting inhibition by heparin via antithrombin
- Similar to thrombin time in measuring conversion of fibrinogen to fibrin

Causes of prolonged time
Year 2005 Paper two: Questions supplied by Ilynn

- All the causes which prolong TT except heparin
- Useful for determining if heparin is cause of prolonged TT

**Activated whole blood clotting time (ACT)**

- Addition of activating agent (eg. Celite, kaolin) to sample of freshly drawn whole blood and measure time (in seconds) for formation of clot
- When heparin concentrations exceed 1.0U/ml (used in CABGs and PTCA), APTT becomes infinitely prolonged
- ACT shows a graded response to heparin concentration in the range of 1 to 5 U/mL

**Lupus anticoagulants**

Presence of antiphospholipid antibody (aPL) produces the LUPUS ANTICOAGULANT PHENOMENON

- Ab against plasma proteins bound to anionic phospholipids
- Cause APTT prolongation
- APTT does not correct after 1:1 dilution with normal pooled plasma in a non bleeding patient
- Adding phospholipid that corrects clotting time confirms presence of lupus anticoagulant phenomenon
- Increased risk of venous and arterial thrombosis

<table>
<thead>
<tr>
<th>APTT</th>
<th>PT (INR)</th>
<th>Common Causes</th>
</tr>
</thead>
</table>
| ↑    | normal  | Intrinsic pathway affected  
|      |         | 1. Von Willebrand’s disease  
|      |         | 2. Isolated deficiencies of factors VIII, IX & XI  
|      |         | 3. Heparin therapy  
|      |         | 4. Lupus anticoagulant phenomenon  |

| normal | ↑   | Extrinsic pathway  
|        |     | 1. Warfarin therapy  
|        |     | 2. Chronic liver disease  
|        |     | 3. Vitamin K deficiency  
|        |     | 4. Factor VII deficiency (rare) |

| ↑   | ↑   | Final pathway affected  
|     |     | Assess thrombin time – if normal common pathway affected  
|     |     | 1. Factor II, V or X abnormalities  
|     |     | 2. Liver disease  
|     |     | 3. DIC  
|     |     | 4. Overanticoagulation with warfarin |

| normal | normal | Pt with apparent bleeding diathesis  
|        |        | 1. Thrombocytopenia  
|        |        | 2. Mild deficiency of VWF  
|        |        | 3. Platelet dysfunction  
|        |        | 4. Factor XIII deficiency |

**Back to the question**

1. APTT, thrombin time increased
2. Normal INR
3. Normal Reptilase time

Intrinsic pathway and the step from fibrinogen to fibrin (final step) affected
Since reptilase time is normal, the answer is **D – Unfractionated heparin**